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CHANGES IN THE SIZE OF THE HEART IN CHILDREN WITH RHEUMATIC FEVER

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REFERRING to roentgenograms of the heart, White[1] points out: "There are so many factors, for example, age, size, build, respirations and nervousness, resulting in individual variations within the normal that it is at present impossible to recognize them all or at least to take them into consideration in the establishment of any satisfactory tables of measurement of normal size. . . . Successive records of heart size and shape in the same individual are more useful than a single comparison of this individual case with a table of normal averages or a set of rules."

Our purpose in this study has been to compare successive roentgenograms, taken at different times on the same patient. In this way the various interfering factors of a constant type are diminished or eliminated. However, there are two sources of error that should be referred to in evaluating roentgenograms of the heart in the same patient. One is the effect of respiration on the shape of the heart shadow, and the other is that of systole and diastole. The latter is slight, and, in older children, a long enough roentgenographic exposure will overcome it. The former factor we attempted to eliminate by catching the patient in the same respiratory phase each time, i.e., the neutral phase. These sources of error obviously have not been ruled out completely, but we believe they have not been sufficient to interfere with the general conclusions which we reached.

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Roentgenograms were taken with the patient standing and the plate 7 feet from the tube. Three standard positions were used: (1) posteroanterior; (2) left anterior oblique, with the patient at an angle of 50°; and (3) right anterior oblique with the patient at an angle of 55° while a swallow of barium was being administered. The posteroanterior position was used in all cases; the other two positions were utilized routinely at first, but latterly only when they appeared to be indicated in more severe cases. The left anterior oblique at 50° was chosen because of the contention of Wilson[2] that at this particular angle the shadow of the heart just clears the vertebral column in the normal subject.

Measurements were obtained from the roentgenograms in the posteroanterior position (P.A.). These included the transverse diameter of the heart (T.D.), the internal diameter of the chest (I.D.), and the cardiac surface area (C.S.A.), estimated by a Diezten planimeter. The body surface area (B.S.A.) was obtained by means of a Du Bois chart from the height and weight.

These results were tabulated for each case, as shown in Table I.

TABLE I

	DATE	HT.	WT. (LB.)	B.S.A.	T.D.	I.D.	C.S.A.	B.S.A. / C.S.A.	NORMAL C.S.A.
Admitted 6/24/39. Dismissed 10/31/39. First attack of rheumatic fever. Mitral systolic murmur which disappeared after six months. Allowed up 9/1/39	6/29/39	5′	103	1.4	15.2	24.0	159	8.7	77-84
	7/18/39	5′	103	1.4	12.5	22.9	104	13.4	77-84
	8/ 3/39	5′	103	1.4	11.5	23.6	92	15.1	77-84
	9/14/39	5′	103	1.4	11.4	24.0	95	14.6	77-84
	10/25/39	5′	106	1.42	11.2	23.2	90	14.9	77-84
	2/16/40	5′1″	117	1.5	11.5	23.9	82	18.2	77-84

In a preliminary study of the question of change in the size of the heart, two particular points were noted with regard to normal hearts that appeared to bear on this problem. The first was the effect of rest in bed on the size of the heart, and the second the effect of heart rate on enlargement of the heart.

Roentgenograms were taken of the hearts of seven surgical patients who had been in bed for four to six months. The ratio of the transverse diameter of the heart to the internal diameter of the chest in these cases varied from 40 to 45 per cent, i.e., all were slightly smaller than the average standard for their height. However, normal standards are difficult to evaluate and further evidence was sought. At this time a patient who had been kept in bed for a year because of a minor abnormality in the electrocardiogram was referred to the hospital. The heart showed no pathologic abnormalities, and the patient was allowed up gradually with no ill effects. Six months later she was well and active and the heart was normal. Roentgenograms of the heart were taken just before she began to get up, after she had been up for two months, and after she had been up six months. These are shown

in Fig. 1*A*, *B*, and *C*. In Fig. 1*A* the heart is obviously small. In Fig. 1*B* it is a little larger, and in Fig. 1*C*, larger again. But even in Fig. 1*C* it is still a little smaller than the average for her height and weight. It was concluded that her heart was smaller than normal because of the bed rest for one year. Since then many other cases have come to our attention, and whenever prolonged rest in bed has occurred (a year or more) the heart appears considerably smaller than normal.

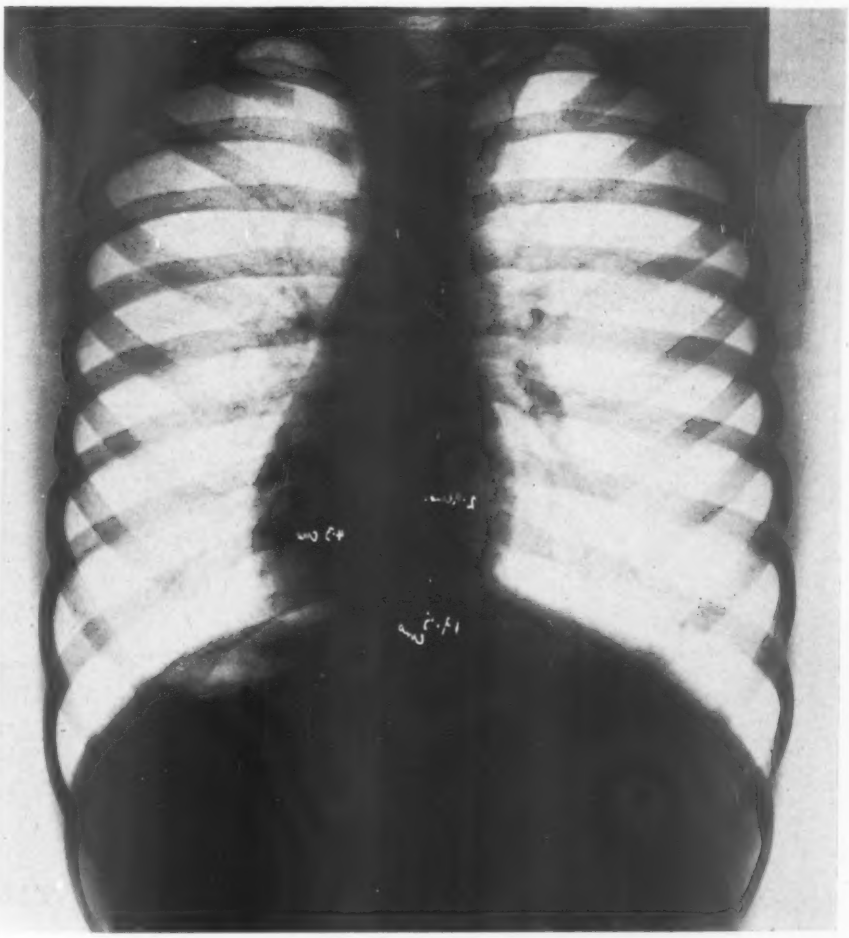


Fig. 1*A*.

Fig. 1.—H. S. had been in bed for one year with normal heart. *A*, Before getting up; *B*, after being up two months; *C*, after being up six months.

The effect of heart rate on the size of the heart was noted in three categories: (1) bradycardia, (2) moderate tachycardia, and (3) paroxysmal tachycardia over 200. Bradycardia was found to produce a slight, but definite, enlargement in a patient with heart block and no

other cardiac defects (see Fig. 2*A*). Moderate tachycardia was found to produce no change in size, even with rates up to 180 or 200 beats per minute.

An interesting case to compare with the one of bradycardia is that of a 12-year-old child who spent two years in bed with hyperthyroidism and a tachycardia of 140 beats per minute continuously (Fig. 2*B*). There was no evidence of heart disease, and a roentgenogram of the heart showed that it was a great deal smaller than normal.

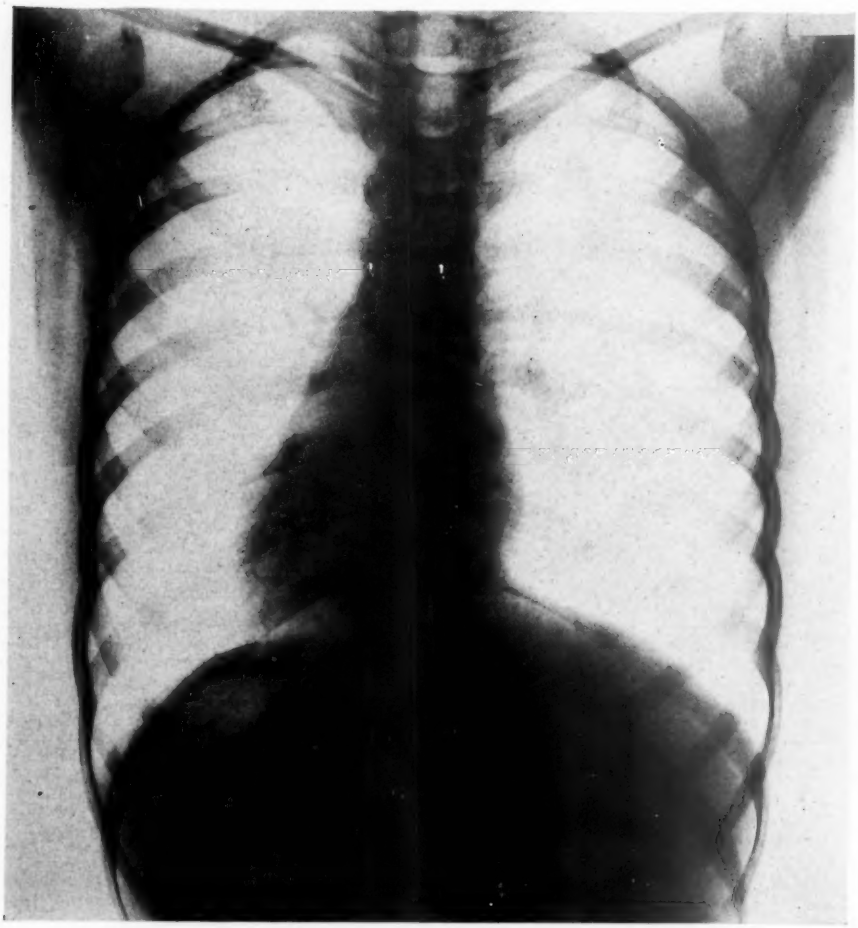


Fig. 1*B*.

In a case of moderate paroxysmal tachycardia reported by Keith and Brown,[3] there was the same lack of effect of tachycardia on the size of the heart. An increase in heart rate, even approaching 200 beats per minute, does not appear to produce enlargement unless it is accompanied by some cardiac lesion.

When the rate is over 200 the effect is variable. Most patients show no enlargement immediately, many do in a few days, and nearly all do if the rate persists at such a high level for one to two weeks or more, particularly if signs of failure have begun to appear. An illustrative case is the following: J. E., 13 years of age, has one or two attacks of paroxysmal tachycardia a year. Roentgenograms of the heart, taken at the time of an attack, have been described in detail in

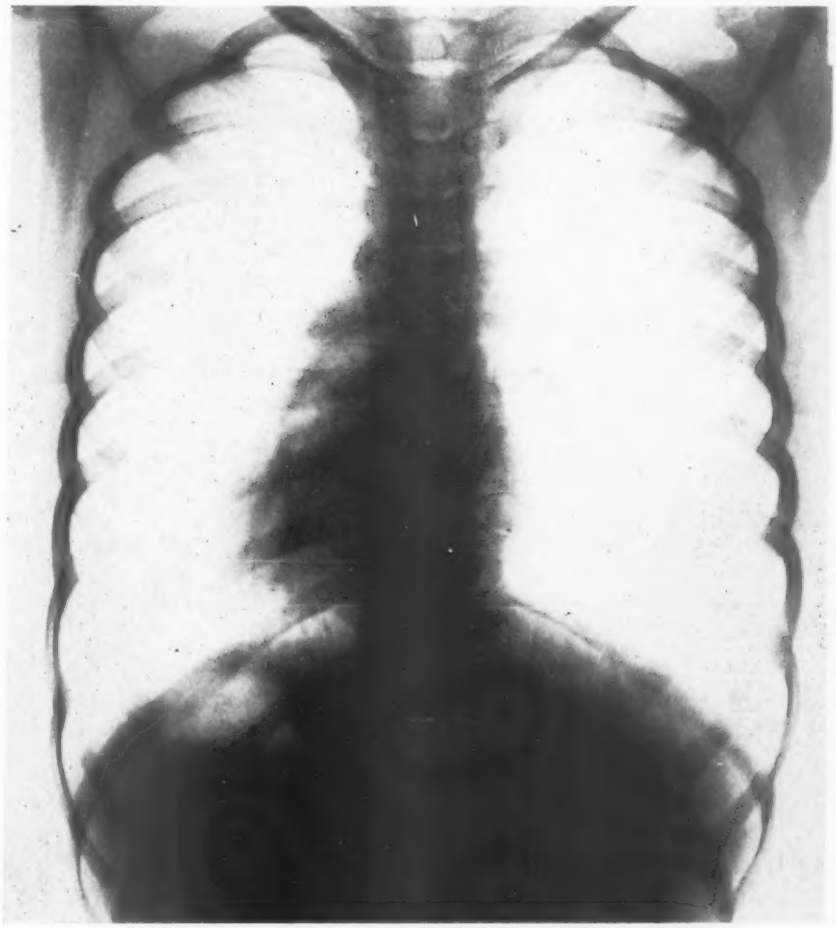
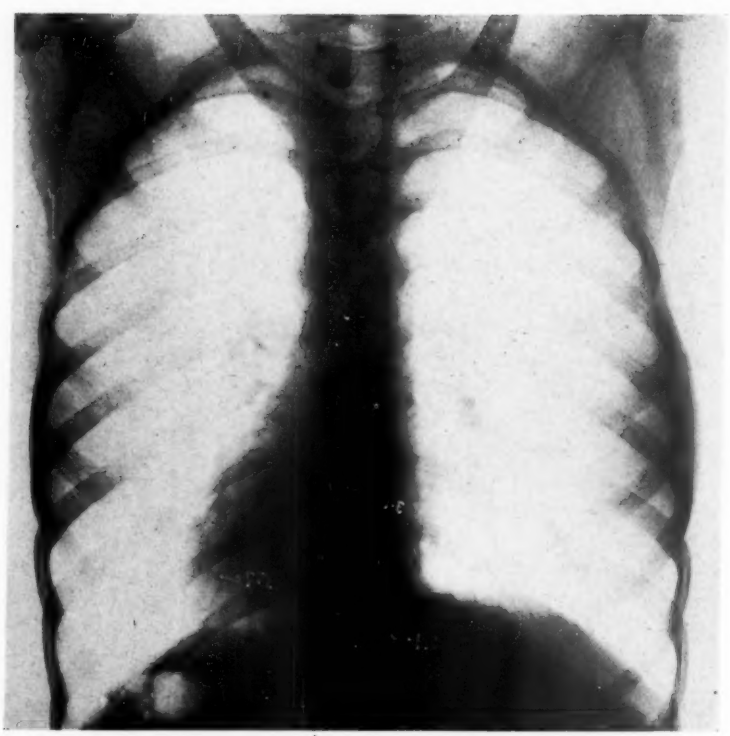


Fig. 1*C*.

a previous publication.[3] The roentgenograms are shown in Fig. 3*A*, *B*, and *C*. The importance of this case lies in the fact that the patient had rapid dilatation of the heart with no disease of the myocardium, and that rapid dilatation may occur within three days and disappear in a week. This leads one to wonder whether such rapid dilatation of the heart can occur when no disease is present, and then, if the myo-

A.



B.

Fig. 2.—*B*, S. H., tachycardia of 140 for two years (hyperthyroidism); *A*, M. D., bradycardia, rate 40 to 50 (heart block).

cardium is affected, as in severe rheumatic fever, whether the same degree of rapid enlargement will develop with the heart beating at a considerably slower rate.

With these points in mind we wished to ascertain how much enlargement of the heart takes place during a single attack of rheumatic fever, and how much smaller the heart may become as the attack subsides.

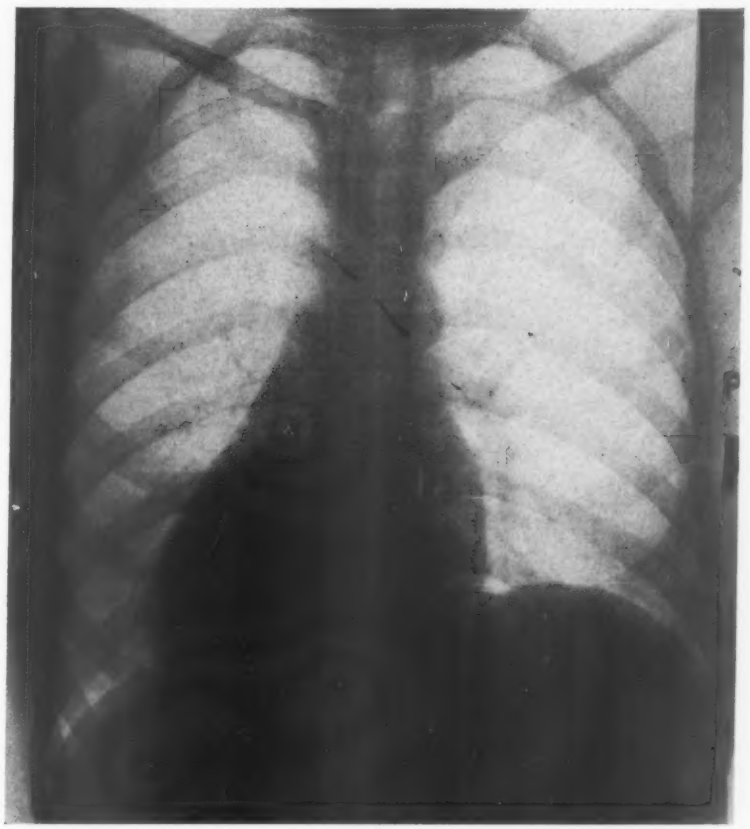


Fig. 3A.

Fig. 3.—J. E., *A*, Normal heart size; *B*, after three days of heart rate over 200; *C*, after two weeks of heart rate over 200.

RESULTS

One hundred patients with rheumatic fever were studied roentgenologically during the various stages of a single attack of the disease. From two to twelve roentgenograms were taken on each patient, the average being four. Ninety-six of the 100 had either rheumatic myocarditis, endocarditis, or pericarditis, and four had doubtful signs of

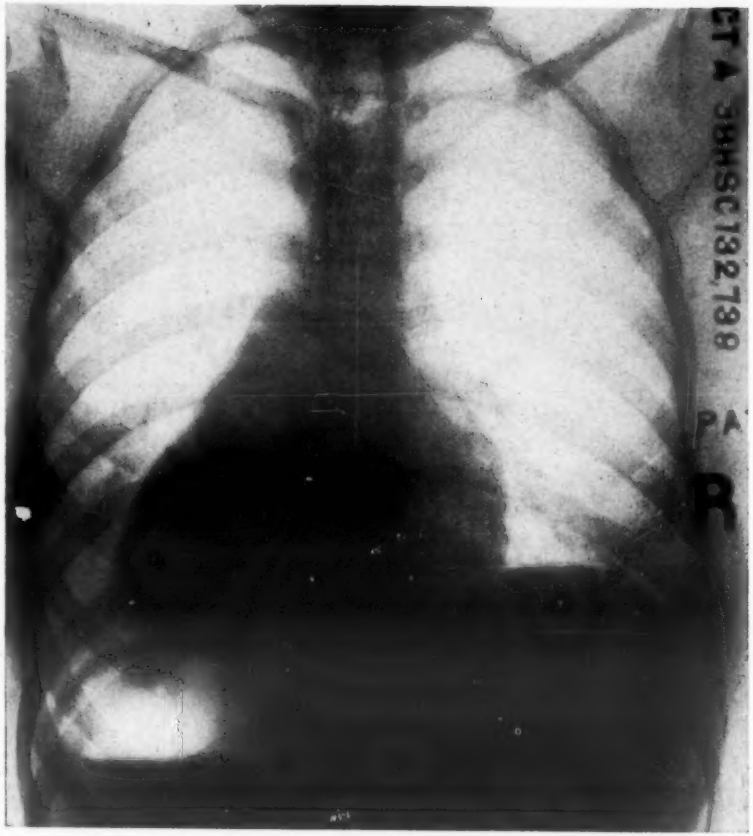


Fig. 3*B*.

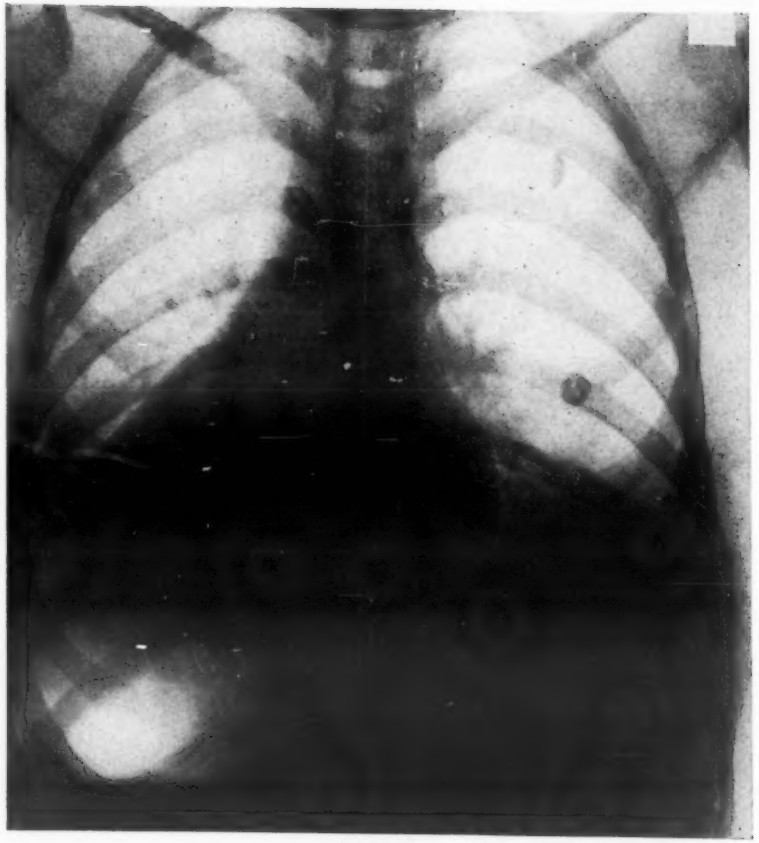


Fig. 3*C*.

heart involvement. The cardiac surface area on admission was compared with the cardiac surface area when progressive change had ceased to occur; that is, the figure set down as representing the alteration in the size of the heart refers to the greatest change during the attack, regardless of whether the heart was getting larger or smaller. This change in size has been set down for each individual case and recorded in chart form (Chart 1).

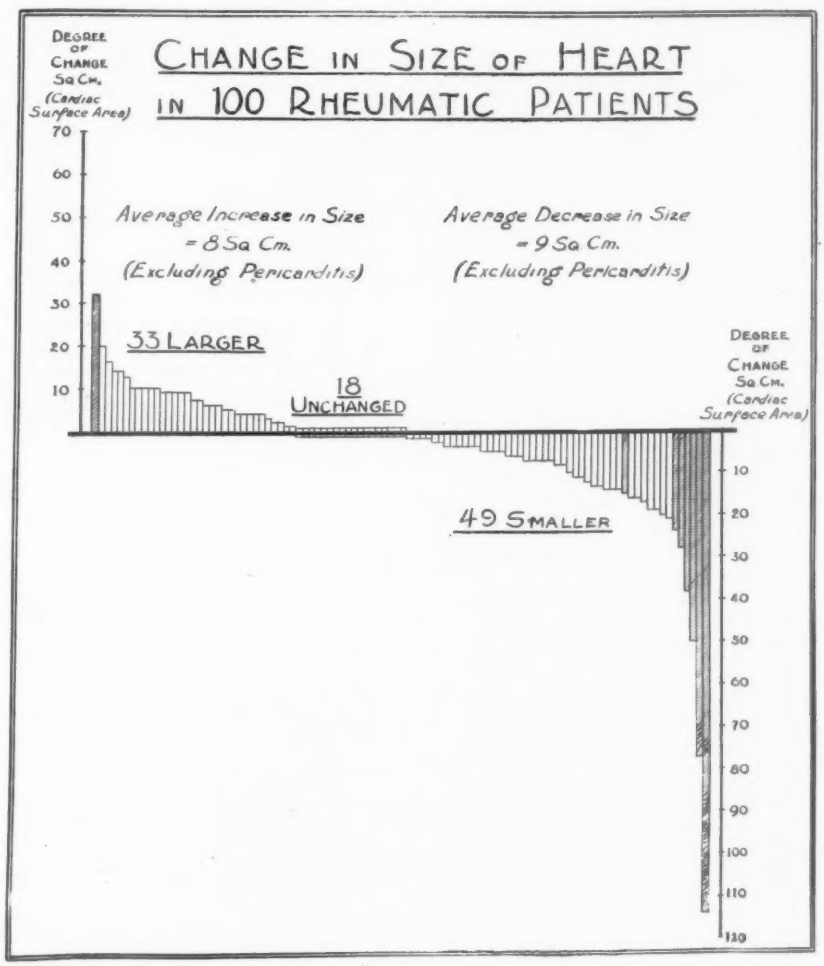


Chart I.

It will be noted that thirty-three of the hearts became larger, eighteen remained unchanged, and forty-nine became smaller. Cross hatching indicates pericarditis with effusion, and it will be seen that this produced the greatest change in the size of the heart shadow. Half of

the hearts became smaller, and a quarter remained unchanged or became only slightly larger. The general outlook in a single attack is relatively good, therefore, although it must be remembered we were unable to include patients who were too ill to be roentgenographed on admission to hospital. Leaving out the cases of pericarditis, the average increase was approximately the same as the average decrease, i.e., 8 sq. cm. as compared with 9 sq. cm. The time required for this change

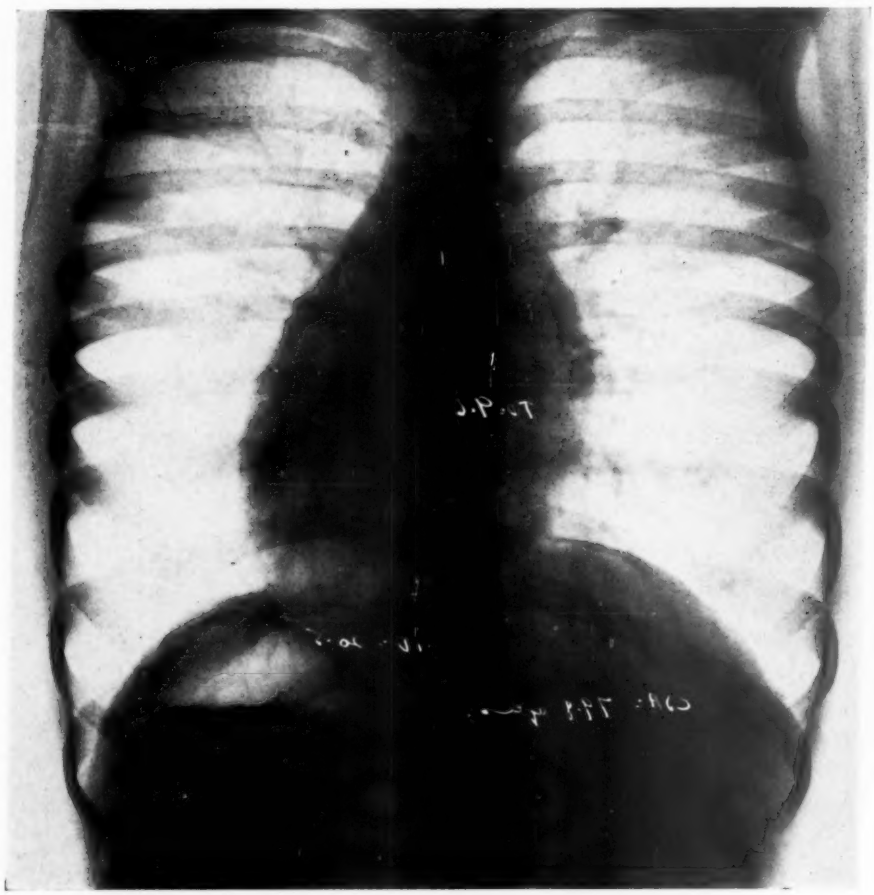


Fig. 4A.

Fig. 4.—J. G., *A*, Heart at beginning of attack of rheumatic carditis; *B*, heart size five months later; *C*, heart size at the end of one year.

to take place was about the same in both groups, namely, 5.8 months as compared with 5.2 months. Change in the size of the heart during rheumatic fever is, therefore, not a sudden, swift process.

The following examples will illustrate the types and variations which were found:

J. G. had three attacks of rheumatic fever within the course of a year. Each attack left her heart notably larger. The third attack produced the greatest degree of enlargement (Fig. 4*A*, *B*, and *C*). It was thought likely that a small pericardial effusion was present, although no friction rub was heard, but most of the increase in size was obviously caused by dilatation and hypertrophy of the myocardium. This case is given emphasis because it shows what tremendous enlargement of the heart may occur in the course of one year.

Fig. 4*B*.

R. W. had an attack of rheumatic fever which was moderately severe. The first roentgenogram (Fig. 5*A*) showed enlargement. In the second (Fig. 5*B*) the heart was about the same size, but improvement had occurred in that the left border was much less prominent. This is an important sign of improvement. The child suffered a relapse shortly after the second roentgenogram was taken, and the third (Fig. 5*C*) showed definite enlargement. The patient ultimately died in this attack.

A. D., aged 12 years, had a mild attack of rheumatic fever with slight involvement of the heart. During his illness the heart enlarged, as is shown by the following:

Date	*Height*	*Weight*	*B.S.A.*	*T.D.*	*I.D.*	*C.S.A.*
8/31/38	5′2″	88½ pounds	1.34	10.3	22.3	102.5
12/15/38	5′2″	113½ pounds	1.48	11.8	22.7	106.7

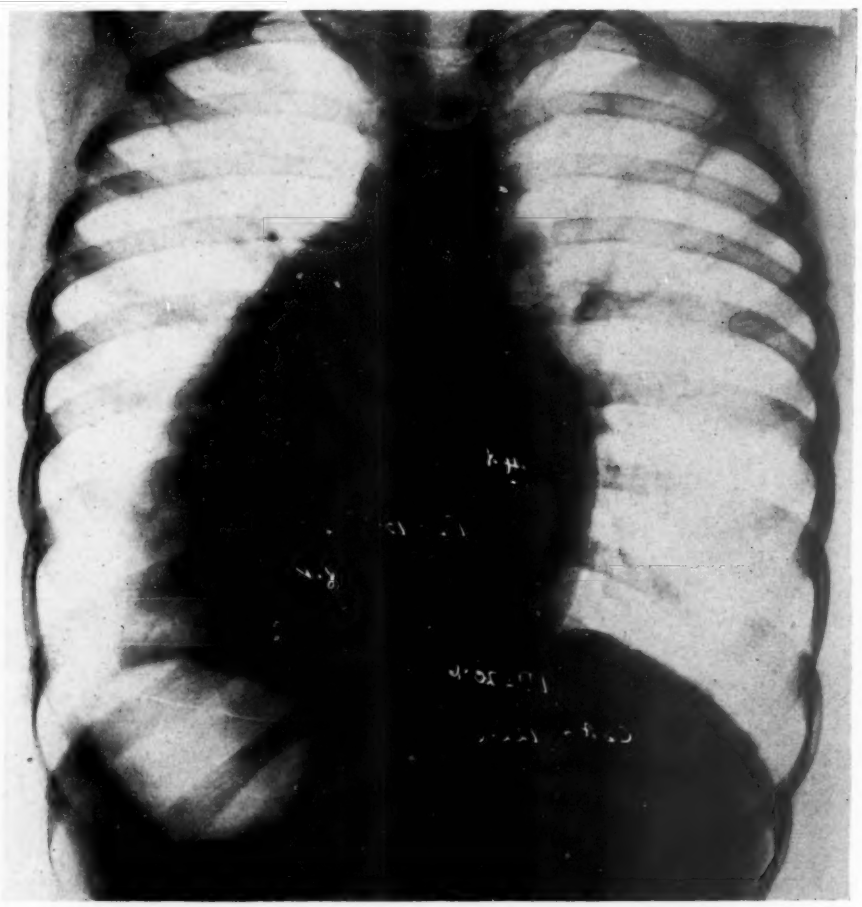


Fig. 4*C*.

J. W. was admitted to hospital suffering from a moderately severe attack of rheumatic fever and carditis. The sedimentation rate was elevated for two and one-half months. During that time the heart became smaller under treatment, but increased again in size when he was allowed to be up (Fig. 6*A*, *B*, and *C*). This increase in size when the patient gets out of bed is a common occurrence, and shows how sensitive the heart muscle is to any increase in work demanded of it. It must be remembered that a normal heart will become smaller with rest in bed, and will then increase again in size when the patient gets up. Therefore, part of the increase in size with exercise may be normal.

L. S. had chorea, coupled with a moderately severe involvement of the heart. On admission the heart was considerably enlarged, and remained so for the first

month in hospital; thereafter it steadily became smaller. Over the succeeding three months the decrease was very marked, as is indicated in Fig. 7. This is as great a diminution in the size of the heart as we have seen after an acute attack and over the short period of three months. This patient has done exceedingly well, and now, one and one-half years later, no longer has a murmur. The heart measurements are within the limits of normal.

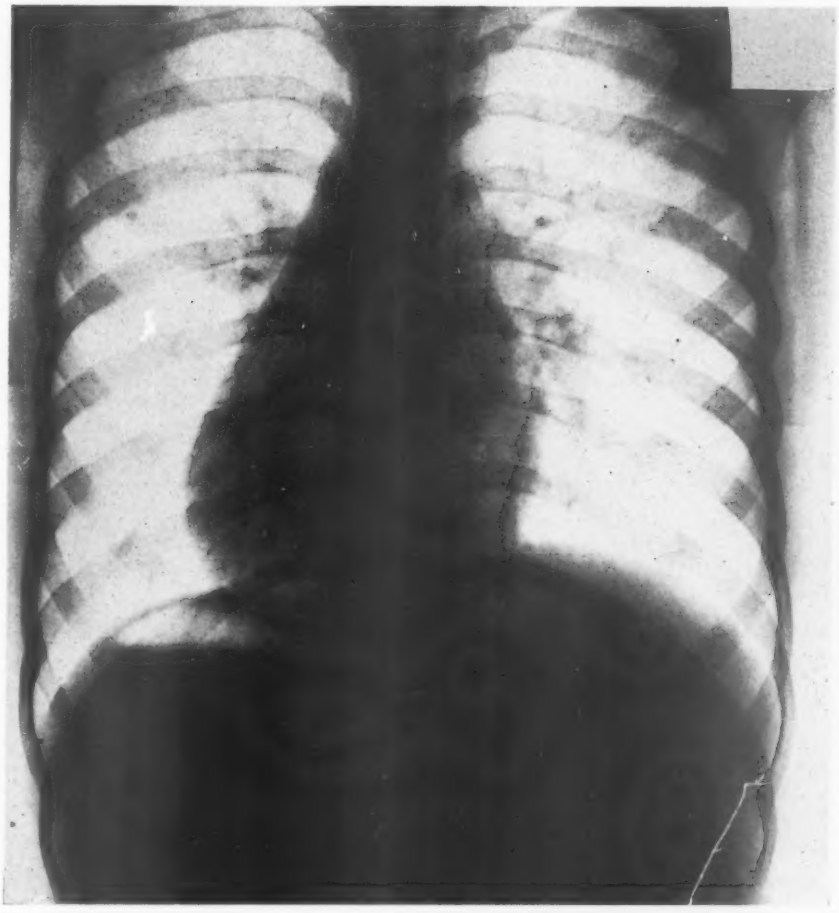


Fig. 5A.

Fig. 5.—J. G., *A*, Enlargement due to rheumatic carditis; *B*, heart has decreased in size in three months; *C*, recurrence of infection produced further enlargement, two months later.

J. B., 12 years old, was admitted with an obvious rheumatic pericarditis. The cardiac shadow was greatly enlarged and showed a rapid decrease in one month (Fig. 8). From our experience, if there is a decrease of 20 sq. cm. in the cardiac surface area in one month, one is almost certainly dealing with pericarditis with effusion. In this case the improvement continued and the heart shadow was within normal limits in three months.

The results shown here indicate a strong ability of the heart muscle to return to a normal condition. With this in mind it is interesting to compare the recuperative power of the myocardium with that of the heart valves. Alterations in the mitral systolic murmur were recorded during the period of roentgenologic study in three groups: (1) murmurs that became louder; (2) those that remained unchanged; and (3) those that became fainter.

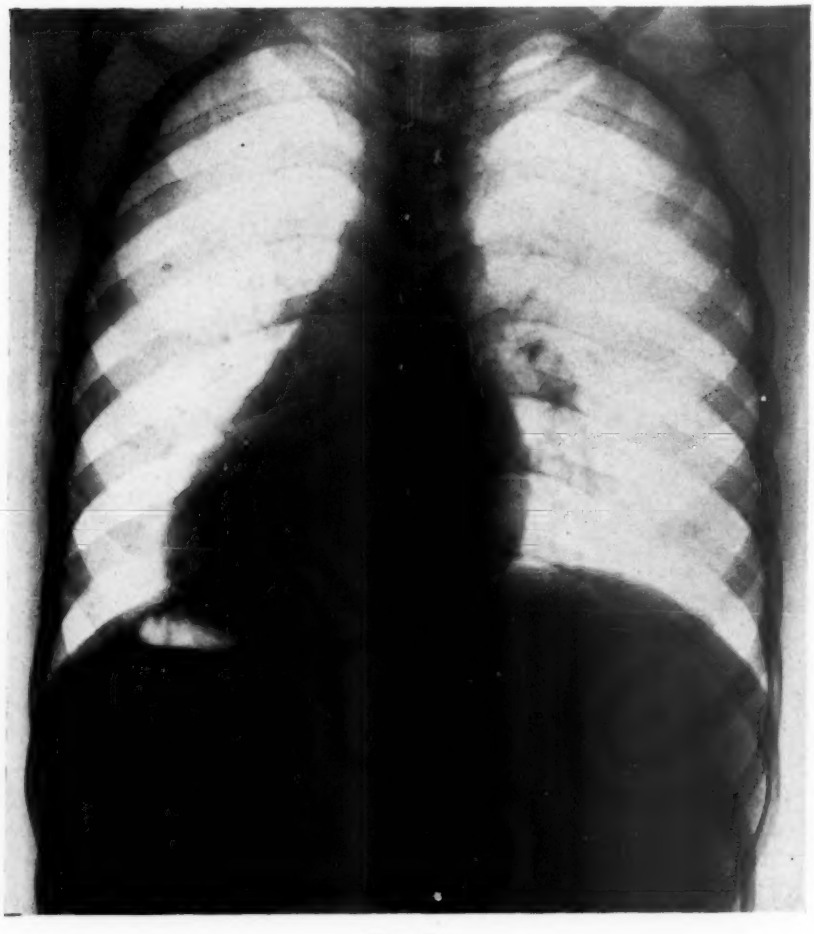


Fig. 5*B*.

The murmur was louder or unchanged in 76 of the 100 cases. This suggests that the restoration of a valve is a much slower process than in the case of muscle. Further evidence of this is the fact that in 60 per cent of the hearts that became smaller there was no change in the murmur or the murmur became louder. Finally, in 8 cases the murmur became louder while the heart was getting smaller. An example of this is the case of R. A. (Fig. 9). He had a moderately severe attack of rheu-

matic heart disease, and over a period of many months his heart became much smaller. At the same time the mitral systolic murmur became harsher and louder. In recent years we have been inclined to overemphasize the muscle damage. We should remember that, because of the persistence of the valvular scar tissue, when the next attack of rheumatic fever occurs an added strain is placed on the redamaged muscle, and the prognosis is made that much worse. It is the muscle that finally fails, but it is the valve that contributes (sometimes decisively) to the ultimate failure of the muscle.

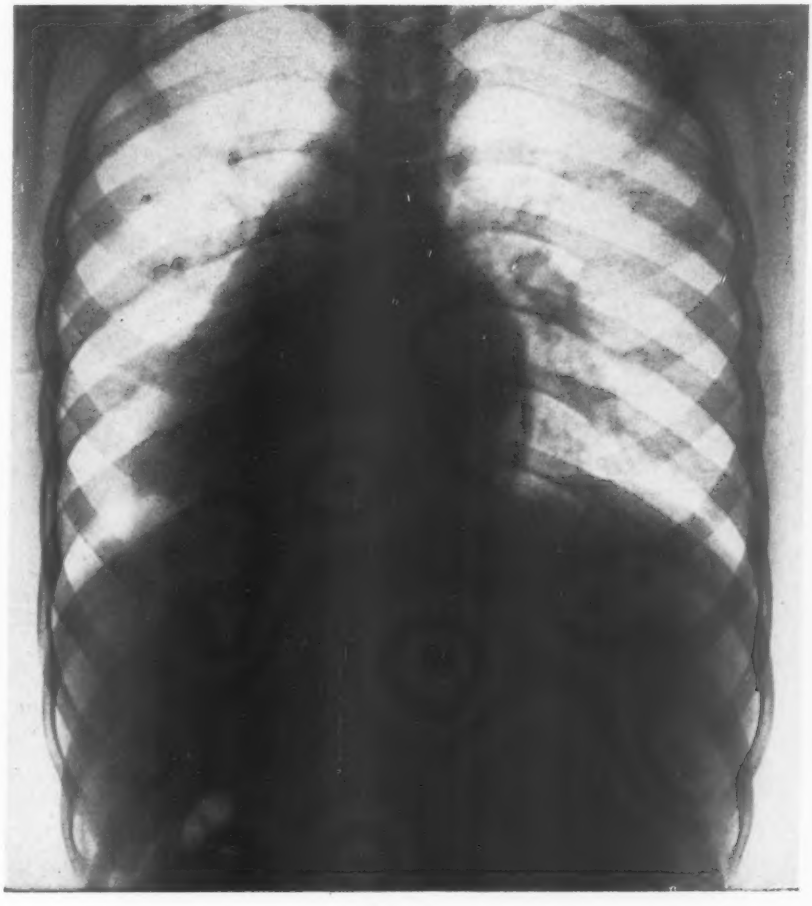


Fig. 5*C*.

COMMENT

The study by Taussig and Goldenberg[4] covered many years, and they divided the patients into three groups, according to the size of the heart: (1) Those whose hearts were not enlarged at the time of the original attack, but became larger over the years, as would be expected with

normal growth. (2) Those whose hearts enlarge with rheumatic infection, and then remain stationary while the chest and the rest of the body catch up; the result is that the size of the heart may ultimately be regarded as normal. (3) Those that show progressive enlargement of the heart beyond the degree anticipated by normal growth.

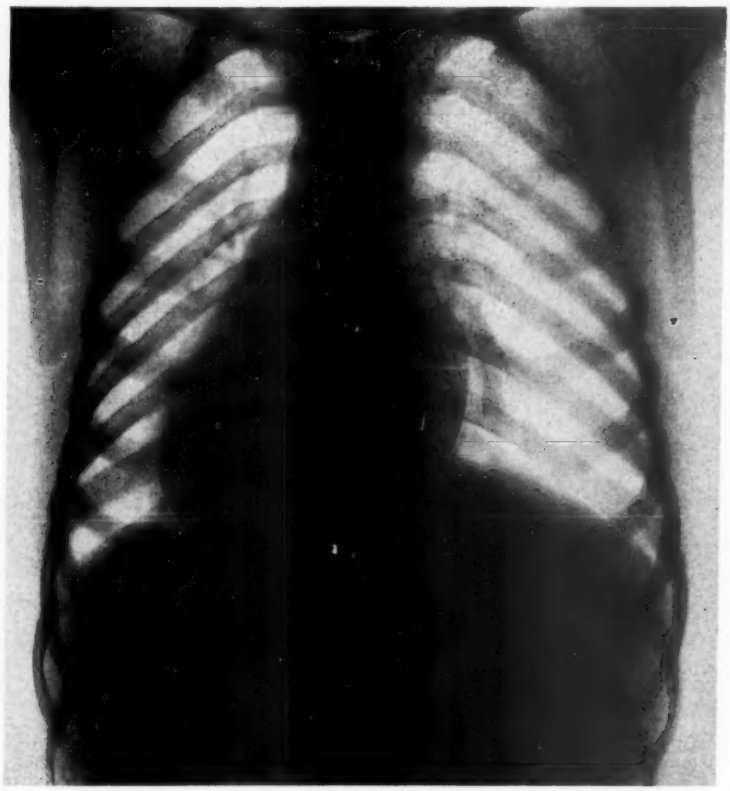


Fig. 6A.

Fig. 6.—J. W., *A*, Heart at beginning of attack of rheumatic carditis; *B*, heart size after five and one-half months in bed; *C*, heart size after being allowed up gradually. This roentgenogram is 2 months later.

The balancing factor through their study was that of body growth. In the present investigation, which is confined within the limits of a year, the interval is too short to be influenced notably by growth. It appears likely that one of the factors which is responsible for normal heart growth is modified or withdrawn when a child is put to bed and can no longer run and play. In our study, therefore, the stimulus to enlargement was mainly the rheumatic infection.

Taussig and Goldenberg[4] found that valve damage may occur without cardiac enlargement. Many instances of this have been noted in our study. It follows from this, of course, that one may have active rheu-

matic infection of the heart without any cardiac enlargement. All who had enlargement had accompanying signs of rheumatic activity. Dr. Taussig believes that there is no essential difference between hypertrophy of the heart in response to the abnormal stimulus of disease and the normal stimulus of growth. Her observations emphasize in a refreshing manner the paramount importance of rest to the heart as long as any abnormal stimulus is present. It is our belief that if life could be maintained with 10 to 20 heart beats per minute, the resulting rest would probably eliminate rheumatic muscle and valvular disease as causes of death or crippling.

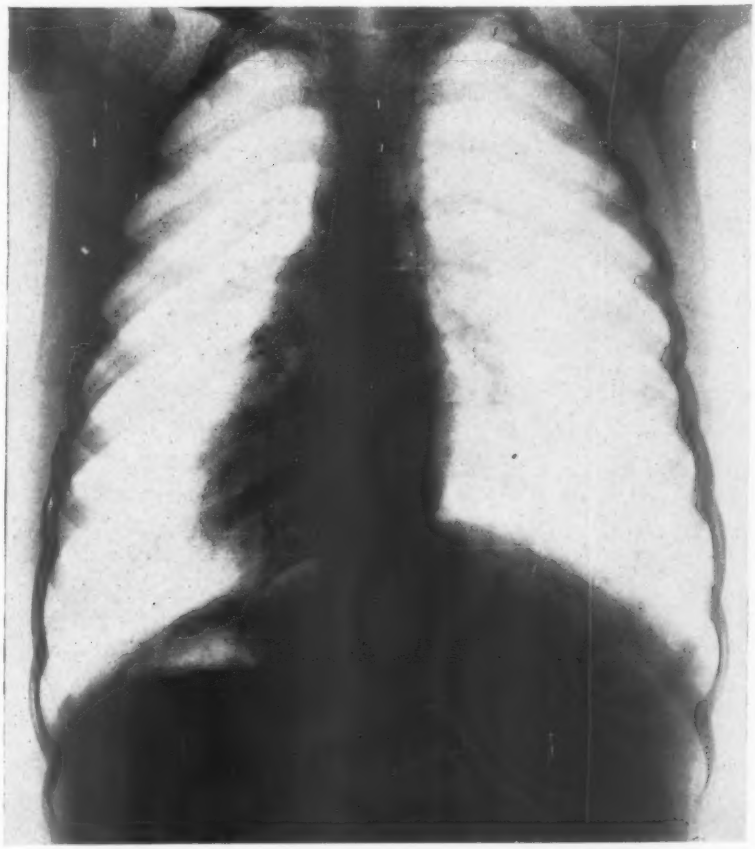


Fig. 6*B*.

During the course of our investigation the superiority of the roentgenologic method over clinical examination frequently made itself evident. The limitations of roentgenology are not nearly as great as those of palpation and percussion. A difference in rate or force of beat will often simulate a change in the size of the heart. It may be

difficult to evaluate a roentgenogram of the heart when it is close to normal, but small changes in size can be much more accurately detected radiographically than by physical examination. Furthermore, the roentgenogram constitutes a record that can be kept for further reference, whereas cardiac size, as estimated by clinical methods, is difficult to remember and record.

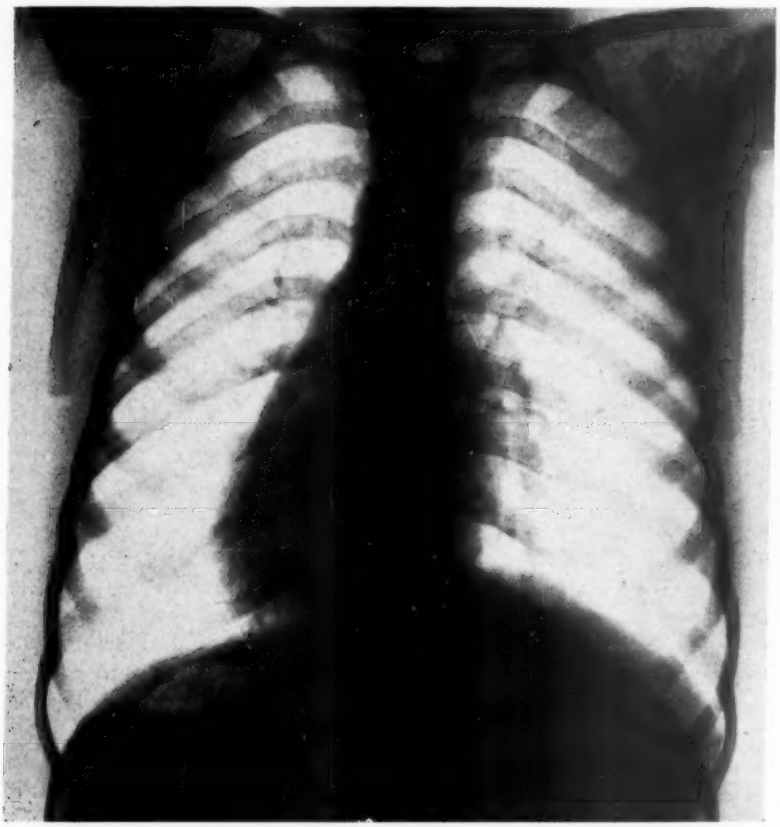


Fig. 6*C*.

In the past, autopsy has often revealed pericarditis when the diagnosis was not made during life. A friction rub may not be heard in more than about 20 per cent of such cases, so that we look to roentgenologic examination for further diagnostic aid. There are two chief points in the diagnosis: (1) the shape of the heart, and (2) the rapid changes in size. The first is exemplified by an enlarged cardiac shadow which is particularly prominent in the left upper border, and is usually surrounded by evidence of mild atelectasis and congestion of the lungs. We have found the cardiohepatic angle of little value in the diagnosis. The second factor has been studied in this investigation. It has been

found that if the heart shadow decreases rapidly in size in one month (20 sq. cm.), it is almost invariably because of absorption of pericardial fluid. In this way a suspicion can be confirmed. Dilatation of the heart, on the other hand, even with the most rapid recovery, takes longer than this.

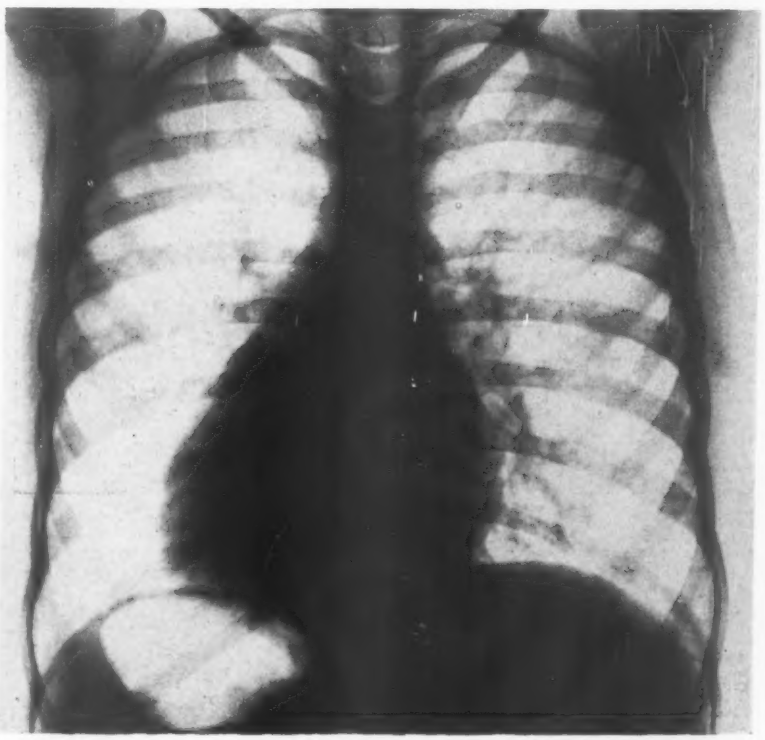


Fig. 7A.

Fig. 7.—L. S., *A*, Enlarged heart due to rheumatic carditis; *B* and *C*, marked decrease in size with treatment over a period of three months.

A problem that continually made itself evident during this study was that of the differential diagnosis of carditis and valvulitis. We have depended on the presence of a heart murmur to make a diagnosis of myocarditis, as well as endocarditis, but the murmur may be caused by either or both. An attempt to differentiate these two is a refinement in diagnosis that should be studied further. The following points were set down during the course of the investigation and are presented with the hope of stimulating criticism:

A. Myocarditis. (1) Enlargement of the heart, i.e., an increase in size over a short time, as shown in repeated roentgenograms, or a definite increase over normal. (2) An apical systolic murmur, blowing in quality, which appears during a rheumatic attack is presumptive

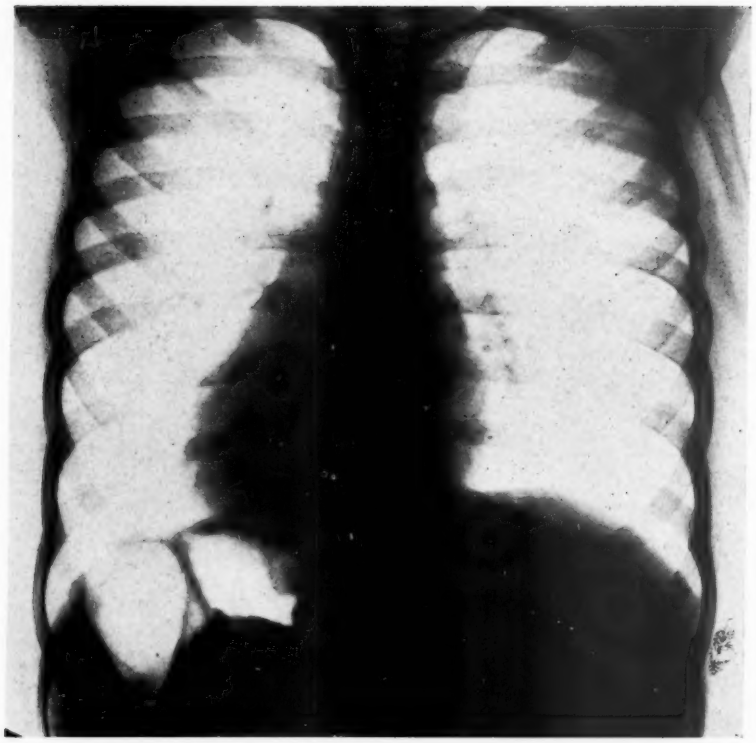


Fig. 7B.

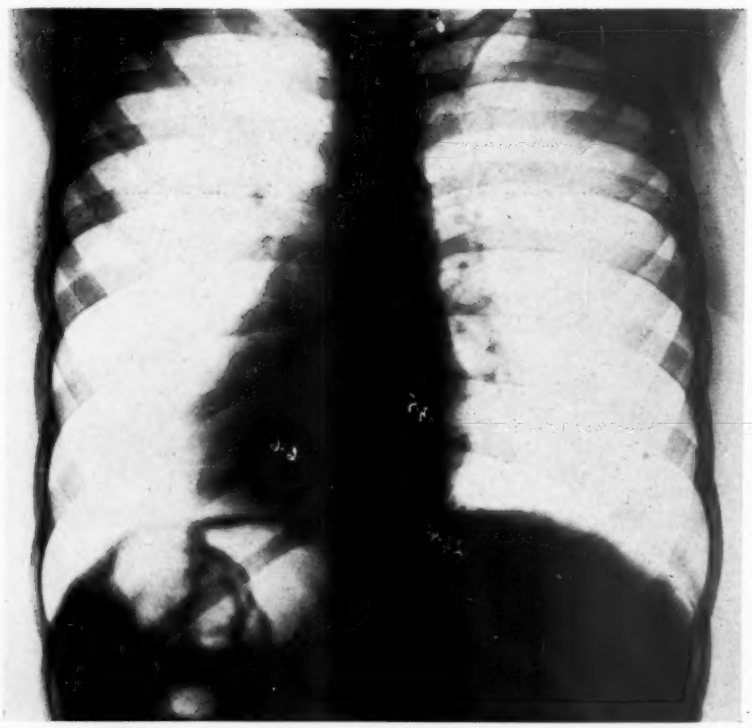


Fig. 7C.

evidence of myocarditis. If the murmur disappears within four months, it is evidence that the myocardium has been affected without involvement of the valve. (3) Increase of the P-R interval of the electrocardiogram above 0.18 second during an attack of rheumatic infection. (4) Accentuation of the third heart sound is probably evidence of myocardial disease.

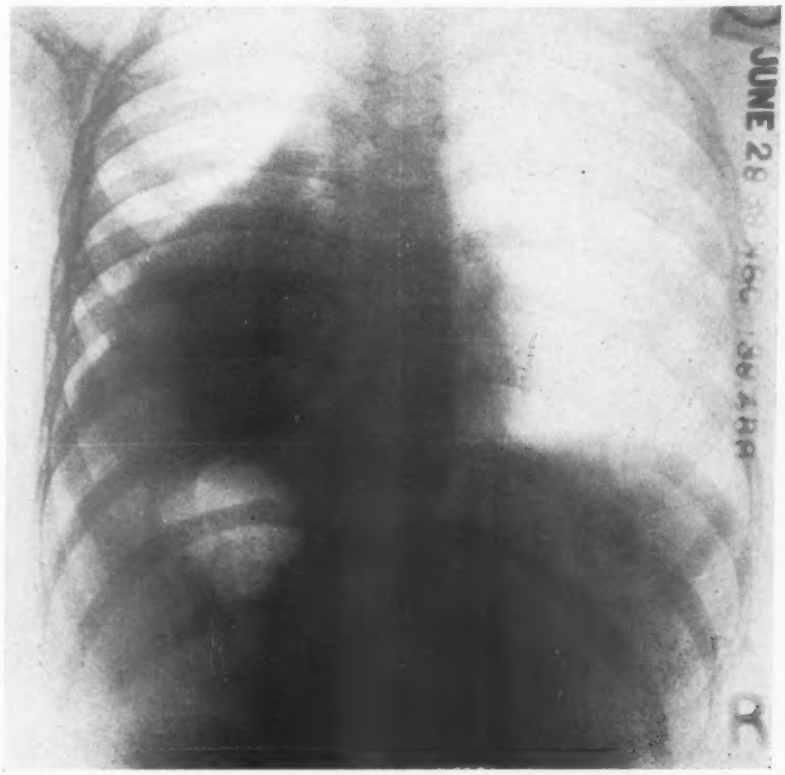


Fig. 8A.

Fig. 8.—J. B., *A*, Enlargement of heart shadow due to rheumatic pericarditis; *B*, taken three weeks later; *C*, taken two weeks later again, indicating very rapid absorption of the fluid.

B. Valvular disease. (1) Apical systolic murmur, transmitted to the axilla, which has been present for four months. (2) A mitral diastolic murmur. (3) Aortic diastolic murmur which has been present for four months. (4) A soft, lightly blowing systolic murmur at the apex may be due to dilatation, whereas a harsh apical systolic murmur suggests valvular damage.

Table I indicates the notable ability of the size of the heart to return toward normal. This depended mainly on rest in bed. In general, it was related to subsidence of the rheumatic infection, but enough hearts became smaller while infection persisted to show that this is not con-

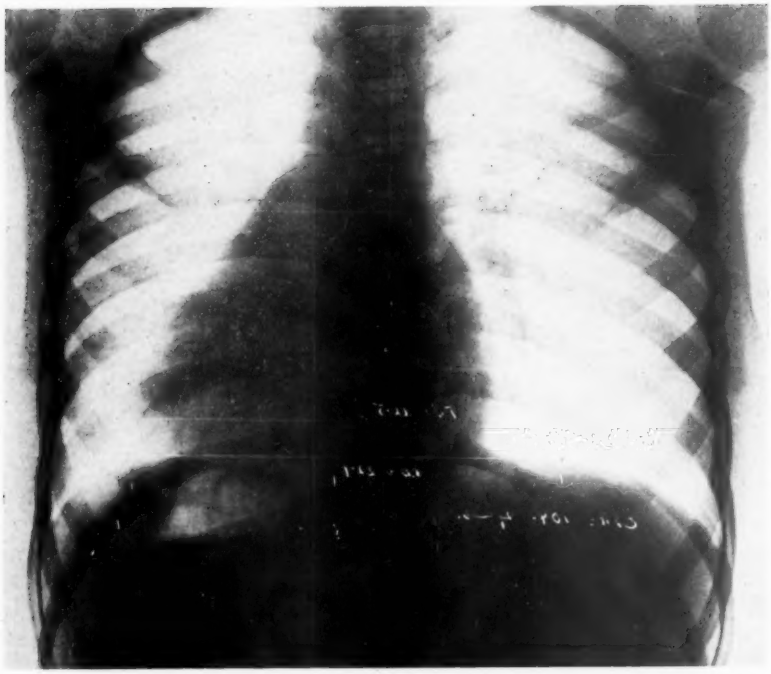


Fig. 8*B*.

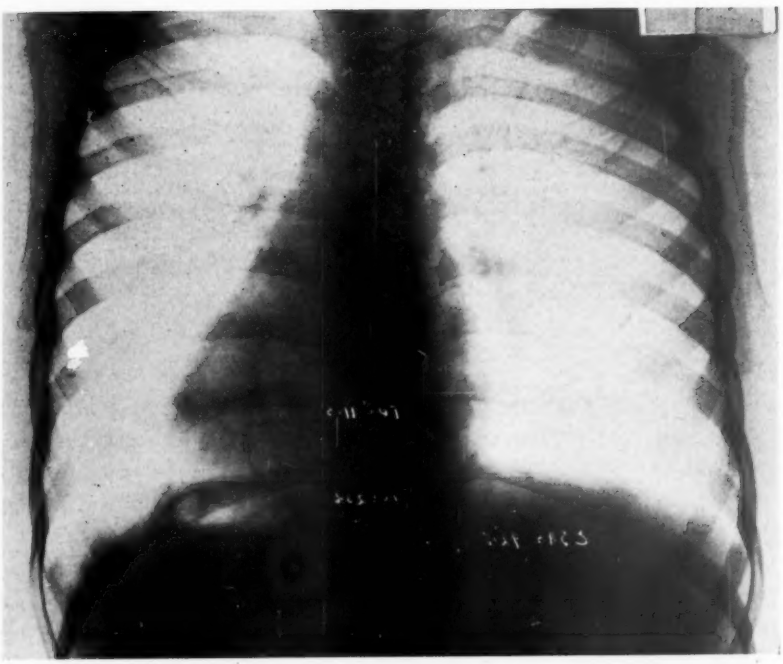


Fig. 8*C*.

tinually so. Many cases impressed us with the shortness of the time in which a decrease in size took place; it was often in a few months, rather than a year or two. In these patients the enlargement must have been caused by dilatation of the heart.

Fig. 9A.

Fig. 9.—R. A., *A*, *B*, and *C* show a steady decrease in heart size in rheumatic carditis. At the same time the mitral systolic murmur became steadily louder and better transmitted.

However, the term dilatation should be used in rheumatic heart disease with caution and a true perspective, because a rapid change in the size of the heart over a few days does not appear to occur except on rare occasions. It is possible that an overwhelming, rapidly fatal rheumatic infection may cause more obvious acute dilatation than was shown in this group, but we could not make roentgenograms in such cases. The patient (J. E.) with paroxysmal tachycardia, with a rate of 240 beats per minute, showed that a marked dilatation can occur in three days. However, such instances are few and far between, and

the general run of hospital cases represented in the 100 instances tabulated here reveals none with such rapid enlargement. Table I indicates that regardless of whether the heart enlarges or becomes smaller, it usually takes three to five months for considerable alteration to become apparent. When the heart is at rest and the infection is subsiding, the maximum decrease may be expected. When active infection continues and the patient is not put to bed, the maximum enlargement of the heart may be looked for.

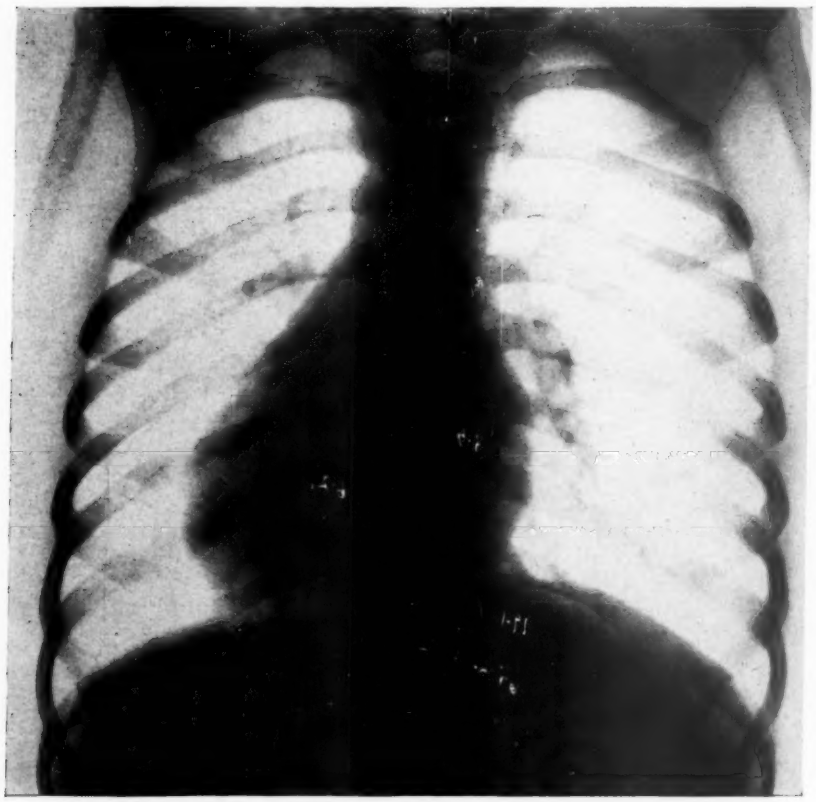


Fig. 9*B*.

SUMMARY

1. It is very difficult to ascertain degrees of change in the size of the heart by physical examination alone. Roentgenologic examination gives more accurate data.

2. Acute dilatation, with a dramatic change in the size of the heart, does not seem to occur (except under rare circumstances).

3. A moderate, initial increase in the size of the heart can take place within two or three weeks, but enlargement appears to occur slowly at any stage of the disease.

4. A fairly marked increase in the size of the heart may occur in five or six months, but the average change in this time is not great.

5. A notable decrease in size may occur in five months, but the usual change in this interval is not great.

6. When change in size in one month is more than 20 sq. cm. in the cardiac surface area, pericarditis is probably present.

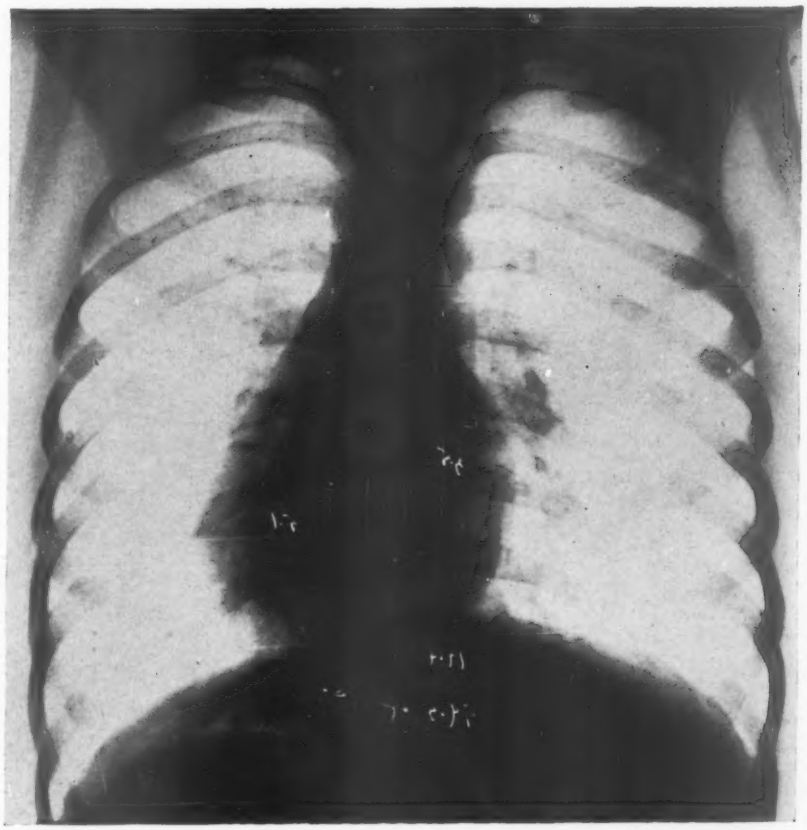


Fig. 9C.

7. The prognosis is obviously better, on the whole, if heart is getting smaller, rather than larger.

8. The heart muscle shows greater recuperative powers than the heart valves. Improvement is more striking in the muscle than in the valve.

9. Roentgenologic examination aids in differentiating between myocardial and valvular disease.

10. In most cases the progress of a patient can be estimated better by studying the size of his heart than by studying the murmur.

11. Bradycardia is more likely to produce cardiac enlargement than tachycardia (certain cases of paroxysmal tachycardia excepted).

12. Continued rest in bed reduces the size of the heart when no disease is present.

REFERENCES

1. White, Paul: Heart Disease, New York, 1937, The Macmillan Co.
2. Wilson, M. G.: Diagnosis of Heart Disease in Children, J. A. M. A. 110: 501, 1938.
3. Keith, J. D., and Brown, Alan: Paroxysmal Tachycardia, Am. J. Dis. Child. 59: 362, 1940.
4. Taussig, H. B., and Goldenberg, M.: Heart Size in Childhood, AM. HEART J. 21: 440, 1941.

LUTEMBACHER'S SYNDROME AND A NEW CONCEPT OF THE DYNAMICS OF INTERATRIAL SEPTAL DEFECT

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LUTEMBACHER'S SYNDROME

THE coexistence of an interatrial septal defect and mitral stenosis is not frequently encountered. Martineau,[1] in 1865, reported the first case. In 1916, one year after Maude Abbott reported a case,[2] Lutembacher[3] summarized the reports available up to that time, offered a concept of the probable genesis of these lesions, and discussed the effect upon cardiodynamics. The presence of both interauricular septal defect and mitral stenosis has consequently been designated as Lutembacher's syndrome. The paucity of case reports in the earlier medical literature can be appreciated by the fact that when McGinn and White[4] reviewed the subject in 1933, and added a case of their own, the total number of cases was twenty-four. Since then, isolated reports by Jerofejeff,[5] Mitchell and Bauer,[6] Kirschbaum and Perlman,[7] and a review of eleven additional cases by Tinney[8] have appeared.

The initial series of twenty-four cases contained only two males, Söldner's,[9] and McGinn and White's.[4] This disparity in incidence between the sexes, however, is less evident in subsequent reports. At present, with this case, there are in all twelve males and twenty-seven females.

This syndrome is not incompatible with prolonged life. Firket,[10] in 1880, described the case of a 74-year-old woman who had survived eleven pregnancies. Lutembacher[3] reported another case in a woman, aged 61 years, who had had seven pregnancies. Sailer's patient[11] lived to be 67 years, and our case is that of a man who is 60 years of age. Generally speaking, however, the life expectancy is considerably less. Eleven of the twenty-four patients in the McGinn and White series died on or before reaching the age of 30; the average age at the time of death was 35.

ORIGIN OF THE SEPTAL DEFECT AND THE MITRAL STENOSIS

The lesion in the interauricular septum is readily explained embryologically. Thin, sickle-shaped membranes, arising from the endocardial cushions, one on the dorsal, the other on the ventral, portion of the

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atrial part of the original single atrioventricular canal, grow downward and unite in the midline, forming right and left atrioventricular canals. From the atrial roof the septum primum grows downward to attach to this newly formed ridge between the canals. Meanwhile the septum primum becomes thinned and perforates in a previously intact region, thereby forming foramen ovale I. In the seventh week of fetal life, a second septum makes its appearance just to the right of the septum primum. It is incomplete, and its foramen is known as foramen ovale II. The growth of these two partial atrial septa is such that the main expanse of the septum primum overlaps foramen ovale II. It serves as a flap which permits blood to pass from right to left, but not in the reverse direction. This condition obtains until after birth, when there is a decrease in pressure in the right auricle and/or an increase in pressure in the left auricle, and the two membranes become closely apposed and gradually fuse into a single atrial septum.[12]

Failure of the septum primum to descend or to attach properly, or a persistent defect in the septum primum or secundum lays the groundwork for Lutembacher's syndrome.

The question of the origin of the mitral lesion, i.e., whether it is congenital or acquired, was at one time much mooted, but now there is almost general agreement that it is acquired. Early, Lutembacher,[3] postulating a congenitally stenosed mitral valve, felt that the elevation of pressure in the left auricle caused by the stenosed valve prevented proper closure of the foramen ovale, and hence caused a reversal of the usual flow through the fetal heart. Firket[10] was of the opinion that the combination of congenital mitral valve deformity and abnormality of the interauricular septum was a fortuitous coincidence which served to safeguard against the pulmonary congestion that would result from the mitral lesion alone. Dressler and Roesler[13] are proponents of the theory that an increase in left auricular pressure, such as probably occurs after birth, would favor closure of the foramen ovale because of the oblique course of the canal. Furthermore, they hold that a small, congenital, interauricular septal defect, complicated by an acquired mitral stenosis, would in time become much enlarged because of dilatation resulting from the increase in pressure within the left auricle. McGinn and White are in agreement with these authors.

A definite history of rheumatic fever was obtained in three of the twenty-four cases reviewed by McGinn and White. The absence of a rheumatic fever history does not militate against the likelihood of acquired endocarditis in these cases, for many patients with proved rheumatic endocarditis never give histories of having been ill with rheumatic fever. In the clinical experience of Dr. George Fahr, Chief of Medicine at the Minneapolis General Hospital, about 25 per cent of the cases lie in this category. Pathologists report figures up to 50 per cent for this group.

The interesting observation of Maude Abbott[14] that atrial septal defects are frequently associated with abnormalities in the structure of the mitral valve leaflets suggests the possibility that disturbed stress-strain phenomena may more readily predispose these leaflets to rheumatic endocarditic changes. Almost three-fourths of Roesler's[15] 62 patients with interatrial septal defect also had chronic valvular lesions.

DIAGNOSIS

Clinically, the diagnosis is a difficult one. The auscultatory signs are quite variable, depending upon the degree of involvement of the mitral valve, i.e., degree of stenosis and insufficiency, degree of enlargement of the heart, and the presence or absence of failure. The size of the interauricular defect is a factor which may account for other auscultatory signs at the base of the heart. The electrocardiogram offers only suggestive evidence if right ventricular preponderance and abnormal P waves are present. The clinical data, when correlated with roentgenographic study, however, may point strongly to the diagnosis.

Assmann,[16] and with slight modification, Dressler and Roesler,[13] suggest a diagnostic roentgenologic tetrad consisting of: (1) Extensive right-sided dilatation and hypertrophy; (2) very wide hilar lung shadows; (3) large conus; (4) narrow or hypoplastic aorta.

In two instances the pronounced hilar shadows produced by the marked dilatation of the pulmonary arterial tree led to a mistaken diagnosis of mediastinal tumor. After a poor response to irradiation, one of these patients was operated on, and the mass was found to be an aneurysmal dilatation of the pulmonary artery in which there was a clot.[24]

CASE REPORT

The case is that of a white man who was 60 years of age at the time of his final admission to the Minneapolis General Hospital, Feb. 11, 1941. Only relevant data from the records of hospital admissions and from the post-mortem observations are presented.

When seen for the first time, June 21, 1938, in the Out-Patient Department, the patient complained of occasional dyspnea, choking sensations, and associated palpitation. He gave a history of diabetes mellitus for seventeen years. A systolic murmur was heard at the apex. The heart was found to be slightly enlarged to the left on percussion. The blood pressure was 122/80. The blood, serologic reactions, and urine were normal.

The patient was admitted to the hospital March 7, 1939, complaining of occasional dyspnea on exertion, and of generalized joint stiffness and painful joint motion. These latter symptoms had been present for several years but recently had become progressively worse. A history of what might have been rheumatic fever at the age of 16 was obtained. The heart was enlarged to the left, and a loud systolic murmur was heard over the entire precordium, but loudest at the apex. The blood pressure was 156/78. A roentgenogram of the chest showed enlargement of the heart of the right ventricular type; the transverse diameter measured 15 cm. There were a distinct prominence of the pulmonary conus and

questionable pressure on the barium-filled esophagus. The electrocardiogram showed left ventricular preponderance, with slightly depressed S-T_1 and slightly elevated S-T_3. The P-R interval was 0.22 second. The blood and urine were normal. The patient was discharged after his diabetes had been brought under control and his joint symptoms were relieved.

On Feb. 7, 1940, the patient returned with a severe upper respiratory infection. Basilar râles were heard posteriorly on the left. A loud systolic murmur was heard over the entire precordium, especially at the third and fourth intercostal spaces along the left sternal border. The pulmonic second sound was accentuated. No thrills were felt. The liver was palpable two fingerbreadths below the right costal margin. The blood pressure was 168/78. Roentgenologic examination failed to reveal any evidence of pneumonia; the right-sided enlargement of the heart was again noted.

The patient was admitted to the hospital Sept. 20, 1940, complaining of shortness of breath and choking sensations for three months, and swelling of the ankles for one month. Dyspnea and orthopnea were evident on examination. Bilateral basilar râles were heard. The heart was enlarged to the left on percussion, and a diffuse apical beat was noted. A soft systolic murmur was heard at the apex. The liver was palpable two to three fingerbreadths below the right costal margin, and edema of the ankles was present. The blood pressure was 188/96, and the venous pressure was 26 cm. of citrate solution. Congestion of both lung fields and a small pleural effusion on the left were demonstrated roentgenologically. The heart was enlarged, and the transverse diameter measured 15.6 cm. The electrocardiogram showed, from time to time, nodal rhythm and complete heart block. Partial A-V block, with the Wenckebach phenomenon, was seen in one record. The patient responded to digitalis, and the diabetes was brought under control before discharge.

The patient was admitted to the medical service Feb. 11, 1941, complaining of shortness of breath and swelling of the face, abdomen, and ankles for one month. Cyanosis of the lips, mucous membranes, and nail beds and generalized edema were noted. The neck veins were prominent. Congestive râles were heard throughout both lungs. The heart was enlarged to the left and right by percussion. A systolic thrill was palpable over the apex, and a presystolic murmur, rough in character, followed by a high-pitched, blowing systolic murmur, was heard at the apex. Occasional extrasystoles were noted. The blood pressure was 160/90, and the venous pressure was 30 cm. of citrate solution. A diagnosis of mitral stenosis and insufficiency was made. Roentgenologic examination revealed enlargement of the heart, with definite pressure on the barium-filled esophagus. Bilateral pulmonary congestion was present. The patient responded poorly to treatment, and died three days after the onset of a pneumonic process. Death occurred on April 20, 1941.

*Post-Mortem Examination**.—Evidence of congestive failure was found in the serous cavities, viscera, and peripherally. There was a pneumonic process in the left lower lobe.

Heart.—The heart weighed 440 Gm. There was a small, adherent thrombus in the left auricular appendage. A large defect, low in the interauricular septum, with a diameter of 4 cm., was found. It occupied approximately two-thirds of the interatrial wall. It was oval in shape, and its lower border reached the level of the tricuspid and mitral rings. This defect was not the foramen ovale, for the obliterated foramen could readily be identified somewhat anterior to this defect (Fig. 1).

*The post-mortem report and photographs of the heart were made available through the kindness of Dr. F. C. Andrus, Chief of the Department of Pathology, Minneapolis General Hospital.

The left atrium and ventricle showed little, if any, hypertrophy or dilatation. The right atrium was markedly dilated, and its wall was definitely hypertrophied. The aortic, tricuspid, and pulmonary valves appeared normal grossly. The mitral valve seemed to be composed of three leaflets. There were fewer than the usual number of chordae tendineae, and two appeared to be thickened. The remainder showed no definite thickening or shortening. The valve leaflets were definitely thickened and had rolled edges. The valve was stenotic, and, before the ring was cut, admitted the tip of the small finger with difficulty. The cut surface of the myocardium was relatively normal. Grossly, no fibrosis was seen. There was minimal arteriosclerosis of the right coronary artery. A small hemorrhagic area in the wall of this vessel did not appear to obliterate the lumen to any appreciable extent. The root of the aorta showed a moderate degree of atheromatous degeneration.

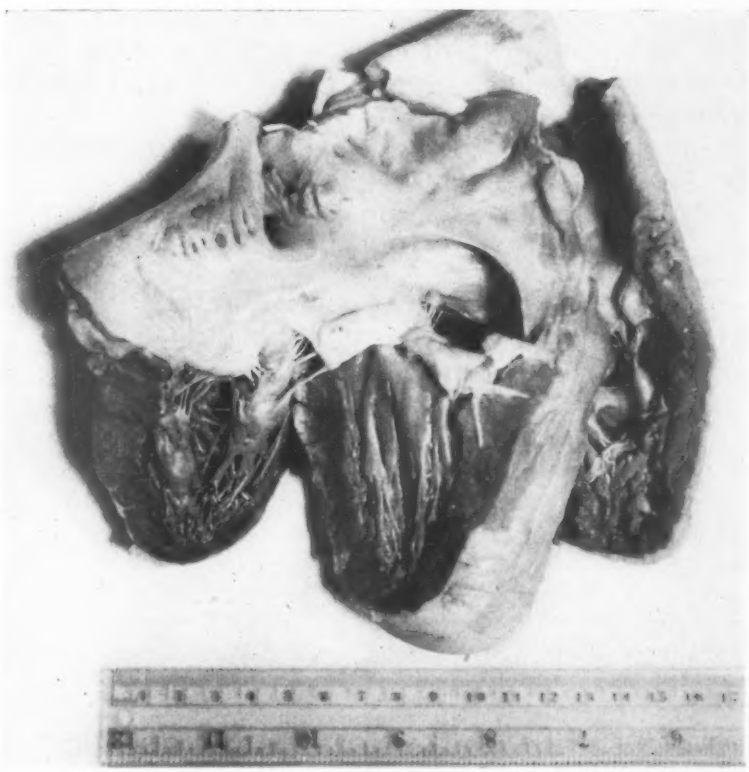

Fig. 1.—The left auricle and left ventricle are exposed to show the thickened, rolled leaflets of the mitral valve, and the split in one of the cusps. The interauricular communication is clearly seen. The thickening and dilatation of the right side of the heart are apparent.

Microscopically, the sections of the heart revealed interstitial edema, as well as slight infiltration with mononuclear cells. There were cellular infiltration and fibrosis about the blood vessels which possibly represented remnants of Aschoff nodules. The mitral valve leaflets showed dense scar tissue, proliferation of fibroblasts, and areas of hyaline necrosis.

Post-Mortem Diagnosis.—Patent interauricular septum primum and mitral stenosis and insufficiency (Lutembacher's syndrome). Pulmonary and generalized edema of congestive failure. Left lower lobe pneumonia.

DYNAMICS OF INTERATRIAL SEPTAL DEFECT

The following discussion is offered in order to correlate the available fundamental data which are necessary for the establishment of a new concept of the dynamic disturbances in Lutembacher's syndrome. However, the concept to be presented applies to all functionally significant interauricular communications, whether or not there is an associated mitral lesion. Since the initial inquiries into the problem were stimulated by a consideration of Lutembacher's syndrome, the discussion will deal first with that entity.

CURRENT CONCEPT

In agreement with Dressler and Roesler,[13] McGinn and White,[4] in the most recent view of the dynamics in Lutembacher's syndrome, explain the post-mortem findings as follows:

"The pressure in the left auricle rises because of the stenosis of the mitral valve, and much of the blood passes through the interauricular septal defect rather than through the stenotic valve. The blood that passes from the right auricle to the right ventricle is then passed through the lungs a second time. The right ventricle and the pulmonary arteries dilate while the aorta remains small because of the reduced volume of blood in the systemic side. The interauricular defect increases in size because of the increased pressure in the left auricle due to the mitral stenosis. The strain is primarily on the right heart, and results in dilatation and hypertrophy. The failure of the left auricle to dilate and hypertrophy subsequent to the stenosis is due to the reduction and equalization of pressure with the left auricle by the septal defect."

OBJECTIONS TO THE CURRENT CONCEPT

The foregoing point of view, however, is a consideration of those changes in cardiodynamics which are incident to the development of mitral stenosis. The phenomena noted are "dated" from the onset of that added pathologic state. Yet important, if not the most significant, structural changes have already occurred in a heart in which an interatrial septal defect is present. For it is more than coincidence that the autopsy findings in cases of interatrial septal defect, either with or without an associated mitral stenosis, are strikingly similar. Generally speaking, in both the complicated and uncomplicated forms, the right auricle and ventricle are markedly dilated and hypertrophied, whereas the left side of the heart undergoes little, if any, change. The branches of the pulmonary arterial tree are considerably dilated, but the aorta tends to become hypoplastic. Hence any consideration of Lutembacher's syndrome must, of necessity, take full account of those antecedent dynamic changes which are caused by the interatrial septal defect alone.

Straub[17] has established the fact that left auricular pressure is greater than right auricular pressure in the normal experimental animal. Roesler,[15] in an excellent, comprehensive analysis of sixty-two cases of interatrial septal defect, contends that this same pressure difference causes a flow of blood from left to right in the presence of a septal defect. Absence of cyanosis in these cases (except terminally) is accepted as prima facie evidence of the direction of flow by Abbott[14] and Roesler.[15] There is little doubt that flow from left to right auricles does occur, but the evidence that this directional flow is caused by a difference in intra-auricular pressures may be questioned.

The flow of blood through the heart is governed by the same principles of hydrokinetics that apply to flow through any hydraulic system. It would be well, therefore, to review the component factors of flow in such a system.

According to the Bernoulli theorem, neglecting friction, the total head, or total amount of energy per unit of weight, is the same at every point in the path of flow in a hydraulic system.* The total head consists of three factors:

(1) The kinetic energy factor, $\frac{v^2}{2g}$

(2) The potential energy factor, h, due to the height above a given datum plane, and

(3) The potential energy factor, $\frac{p}{w}$, or, head of pressure.

The theorem simply states that the sum of these three factors at one point in the stream must be equal to the sum of these factors at any other distal point.

However, since fluids in motion invariably suffer a loss of energy through friction, this loss is accounted for by adding the factor "f," to the right-hand side of the Bernoulli equation. Thus,

$$\frac{v^2}{2g}L + \frac{p}{w}L + h_L = \frac{v^2}{2g}R + \frac{p}{w}R + h_R + f$$

It must be inferred from Roesler's explanation that the energy head in the left auricle is greater than that in the right by virtue of the pressure difference. If this were the important factor, one would expect to find enlargement of the left auricle, perhaps exceeding that of the right. For it is generally accepted that the differences in work demanded of the various chambers of the heart determine physiologic or pathologic dilatation and hypertrophy, or both, of the respective chambers. When there is an increase in pressure within a chamber, that chamber is called upon to do more work than one with a lower pressure.

*It should be noted that the Bernoulli theorem, as stated, applies to any stream in which all particles in any cross section have uniform flow. However, the three factors of the Bernoulli equation which follow are applicable as well to streams of varying cross section and nonuniform velocities, by slight modification of the formula.

This is well borne out by the phenomena which are known to occur during the normal growth of the heart. At birth the walls of the right and left ventricles are approximately equal in thickness; the right is slightly thicker in the ratio of 8:7.[18] In time, the left ventricular musculature increases in thickness. This is the result of the rapid expansion of the systemic vascular bed, which parallels body growth and increases peripheral resistance, and this demands an increased head of pressure in the left ventricle. In contrast to this, the relatively slowly changing resistance in the pulmonary bed makes a much smaller demand on the right ventricle. Because of the disparity in heads of pressure necessary for flow in the distinctly separate circuits, the left ventricular wall becomes measurably thicker than the right within three to four months after birth, according to both Gross[19] and Müller.[20] By the end of the first year of life, this ratio is approximately 2:1.[21]

A change in the auricular musculature must also occur after birth, although to a much less extent than in the ventricles. Auricular systole, which contributes about 5 to 10 per cent to the respective total ventricular blood volumes, occurs at a time when the ventricles are completely filled. Therefore, the final auricular contribution must be expelled with sufficient force to distend further the filled ventricles, and the left auricle must exert a greater ejection force than the right auricle in order to transmit its distending pressure to the heavier muscled left ventricle. Thus there is established the adult ratio of left to right auricular thickness of 3:2 or 2:1.

A comparable "demand-response mechanism" must obtain in the pathologic as well as the physiologic state. Accordingly, if, as Roesler states, the left auricular pressure is greater than the right, and causes a flow from left to right, the left auricle should show a degree of enlargement at least equal to, if not greater than, that of the right. Yet necropsy specimens in cases of interatrial septal defect, whether simple or complicated by mitral stenosis, show marked structural changes in the right auricle, and the left auricle is almost completely spared. Hence, some mechanism other than a pressure difference must account for the ultimate cardiac changes.

NEW CONCEPT OF THE DYNAMICS OF INTERATRIAL SEPTAL DEFECT

A consideration of the various factors in the Bernoulli theorem affords an opportunity to view such possibilities critically. Of these factors, one which has previously been given no consideration to my knowledge is the potential energy factor, "due to the height above a given datum plane."

If one visualizes the projection of a heart in three-dimensional space, noting axial and planar relationships, this new possibility presents itself. For, if the auricular axial plane is such that the left auricle is

placed above the right, and the patent septum lies in the floor of this upper chamber, it is conceivable that a gravitational factor would determine the direction of flow of blood between the chambers. This gravitational shunting of blood would throw a considerable load upon the right side of the heart, and perhaps set up the dynamic state which leads to the characteristic changes in hearts with a septal defect.

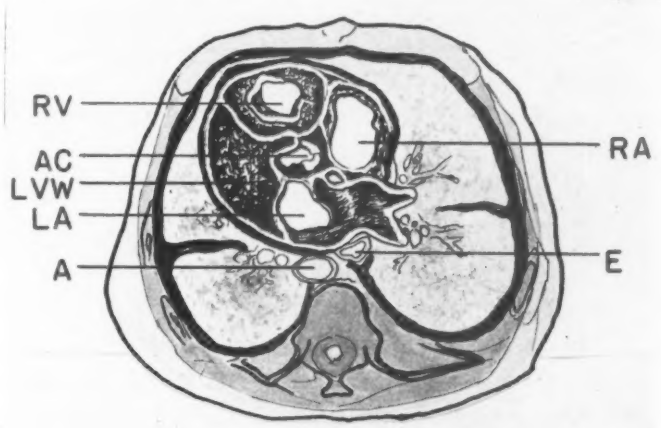

Fig. 2.—Horizontal section viewed from above, at the level of the upper border of the fourth rib (body of newborn infant). *RV*, Right ventricle; *AC*, aortic cusps; *LVW*, left ventricular wall; *LA*, left auricle; *A*, aorta; *RA*, right auricle; *E*, esophagus. This drawing was made from a photograph in the original article, as quoted, and is reproduced with the permission of Dr. J. C. Gittings.

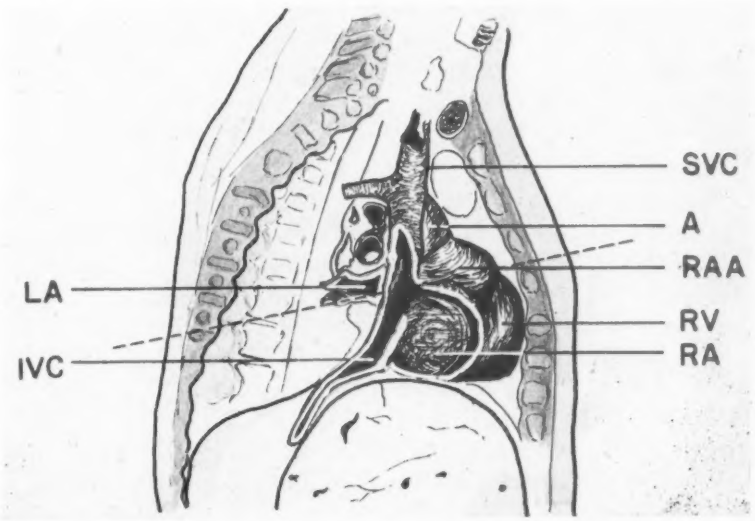

Fig. 3.—Sagittal section, viewed from the right; the plane of the section is 0.75 cm. to the right of the midsternal line (body of newborn infant). *LA*, Left auricle; *IVC*, inferior vena cava; *SVC*, superior vena cava; *A*, aorta; *RAA*, right auricular appendage; *RV*, right ventricle; *RA*, right auricle. The broken line represents the approximate plane of the foramen ovale. Copied from a photograph with the permission of Dr. J. C. Gittings.

About thirty years ago, a classic study on the anatomic relationships of intrathoracic structures in newborn infants was made by Fetterolf and Gittings.[22] The authors injected the bodies with a 10 per cent formaldehyde solution and froze them. Numerous dissections and horizontal and sagittal sections were made through various portions of the thorax. Two drawings from their photographs are here reproduced (Figs. 2 and 3). The first, a horizontal section through the thorax, shows the relationship of the auricles in that plane. The second, a sagittal section, shows the left auricle in a definitely more cephalad position than the right auricle, and, what is most significant, the plane of the foramen ovale. Quoting the authors, "The foramen ovale lies in an almost horizontal plane, and not vertically, as is commonly supposed." Here, then, is anatomic evidence in support of the proposed concept.

AN EXPERIMENTAL PROCEDURE

Simple laboratory methods afford an opportunity to note the flow changes in a two-chamber system with a common patency. Two condoms are rubber-cemented together, while uninflated, and, after cohesion occurs, a communication is established in their common wall. A U tube, with inflow source, is fitted into the proximal free ends, and tubes of smaller diameter are tied into the distal ends (Fig. 4). The two chambers are placed in the same horizontal plane, and the septum, therefore, occupies a vertical plane. The system is filled with water, and, when the inflow rate is sufficient to maintain a slight but unvarying distention of the chambers, that rate is kept constant. It is noted that the trajectories of fluid from the two outflow orifices is identical in pattern and distance. Also, if the escaping fluid is collected in separate containers, it is seen that in a given period of time the volume flows are identical.

The assembly is now turned so that one chamber lies above the other, i.e., the communication is in a horizontal plane (Fig. 4 should now be labeled "seen from the side"). Even though the rate of inflow to the system is kept constant, as before, the lower chamber is seen to dilate slowly, whereas the size of the upper one decreases somewhat. When equilibrium is again established, the pressure in the lower chamber is greater than that in the upper chamber for (1) it is larger; (2) the trajectory from the lower chamber extends beyond that of the upper chamber; (3) the rate of outflow from the lower chamber is greater than that from the upper chamber.* These differences are attributable to the difference in height between the respective streams above a given horizontal datum plane.

*Sample readings at 25 seconds:
Upper chamber outflow, 192 c.c.
Lower chamber outflow, 205 c.c.

Thus we see that if two chambers with a common communication are so disposed that the septum containing the communication lies in a vertical plane, if the inflow rate is constant and the outflow orifices are of the same diameter, there need be no mixing of the contained fluids; in fact, the assembly functions as if there were no communication between the chambers. But when the two chambers are placed in a position so that the communication lies in a horizontal plane, i.e., so that one chamber lies above the other, it is seen that the lowermost chamber dilates, that there is a definite increase in pressure in that chamber, and that an increase in the rate of outflow occurs, with corresponding opposite changes in the upper chamber.

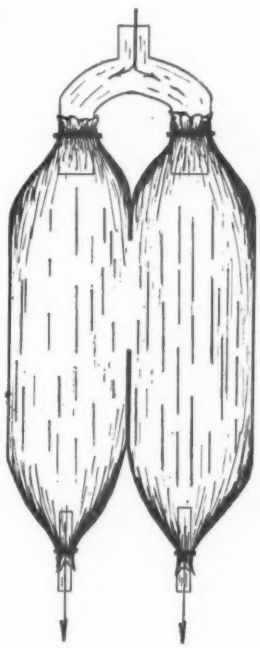

Fig. 4.—Experimental assembly, viewed from above, of a two-chamber system with a communication.

The foregoing theoretical, anatomic, and experimental evidence indicates that the proposed concept is acceptable, so that we may now turn to a consideration of the dynamic effect of the auricular axial plane and the plane of the septal patency on cardiodynamics.

The first year of life is spent almost entirely in a recumbent position. Since the septal defect then lies in a nearly vertical plane, the conditions of the first portion of the model experiment are approached. But with the body in the recumbent position, the right auricle lies somewhat anterior to the left (above), as shown in Fig. 2. One may surmise that this axis is less exaggerated in life, i.e., that the auricular axis is more transverse than is apparent in the sketch, or, that if there is any flow from right to left, it is insufficient to produce cyanosis.

As the upright position is assumed, gravitational flow of blood from the left auricle becomes a certainty, for with that chamber lying cephalad to the right, and with the interatrial septal defect in the floor of the upper chamber, this shunt must function. Filling of the right auricle is accomplished not only by the usual means, but also by the flow-off from the left auricle caused by gravity. The right auricle will dilate in order to accommodate this added load, as will the right ventricle. Eventually, because of the increased flow through it, both chambers of the right side of the heart will hypertrophy. The pulmonary arterial system, which receives an increased volume of blood from the right side of the heart, also dilates. The systemic chambers and vessels, on the other hand, maintain a status quo, or, because they receive less than the usual quantity of blood, undergo regressive changes. This is readily seen in the aorta, which tends to become hypoplastic.

The fundamental "gravitational disposition" of the auricles remains essentially the same, even after the gradual shift of the heart to the so-called "adult position," which is completed between the seventh and tenth years of life.[23] The vicious cycle, therefore, is continuous throughout life, except during the time that the recumbent position is assumed.

If a person with an interauricular septal defect should have one or more attacks of rheumatic fever, with resultant valvular disease, particularly of the mitral valve, the role of this superimposed lesion on cardiodynamics must be considered. The frequent incidence of rheumatic valvulitis in these cases has already been referred to, and, as indicated, is quite common. When an effective mitral stenosis is established, the residual volume of blood that usually causes such profound changes in the left auricle has almost a negligible effect on that chamber. It is obvious that the blood which is prevented from passing to the systemic circuit through the stenotic orifice flows directly into the right auricle, and there merely adds to the increased load on the right side of the heart.

In the light of the foregoing discussion, it is apparent that the heart in Lutembacher's syndrome undergoes essentially the same pathologic changes as the heart which is the seat of an uncomplicated interatrial septal defect. Further, the structural changes in both forms can readily be accounted for by the gravitational disposition of the auricles and plane of the patency between them, without hypothesizing a pressure gradient between the auricles, which, as shown, may be questioned from several standpoints.

SUMMARY

A report of a case of Lutembacher's syndrome (combination of interatrial septal defect and mitral stenosis) is presented. The currently held view of the dynamic changes in such a heart is discussed. It is

pointed out that the fundamental disturbance in dynamics is the same whether or not the septal patency is complicated by a mitral lesion. According to previous investigators, the ultimate development of marked dilatation and hypertrophy of the right auricle and right ventricle, with minor involvement of the left auricle and left ventricle, is caused by shunting of blood through the communication, which in turn results from the fact that the pressure in the left auricle is higher than that in the right. Evidence is presented to show that this explanation is not tenable.

A new concept of the dynamics of interatrial septal defect, based on a correlation between fundamental hydraulic principles and anatomic and experimental considerations, is proposed. It is shown that when two adjoining chambers have a source of constant and equal inflow, a free communication in their common wall, and outflow orifices of equal diameter, the gravitational orientation of the chambers determines their respective sizes, intraluminal pressures, and volume flows. If the chambers are placed one above the other, with the communication in a horizontal plane, the inferior chamber dilates and its outflow trajectory extends beyond that of the upper chamber, which indicates that there is a greater intraluminal pressure in the lowermost chamber.

From an anatomic standpoint, evidence is presented to show that the auricular axis is such that the left auricle occupies a definitely more cephalad position than the right. Further, the plane of the foramen ovale (septal defect) is almost horizontal, and not vertical, as it is commonly represented. With the disposition of the chambers and septal defect in this relationship, filling of the right auricle is accomplished by the usual caval flow, and by a gravitational flow through the communication in the floor of the superiorly placed left auricle. Dilatation of the right auricle results, and, in due time, the right side of the heart shows dilatation and hypertrophy, whereas the left auricle and ventricle, which play almost no role in these events, remain essentially unaffected. The aorta becomes hypoplastic because of the decreased systemic volume of blood. The pulmonary arterial tree, on the other hand, necessarily dilates to accommodate the increased volume of blood in the lesser circuit. The presence of mitral stenosis simply exaggerates the flow differences.

The proposed concept obviates the necessity of postulating a pressure gradient theory to explain the pathologic changes, and offers, instead, a well-correlated explanation of the entire progression of events which are associated with an interatrial septal defect.

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REFERENCES

1. Martineau: Sur un cas de retrecissement mitral avec persistance due trou de Botal, Bull. Soc. d. sc. méd., Clermont-Ferrand, March, 1911.
2. Abbott, M. E.: Intnat. Assoc. Med. Bull. **5**: 129, 1915.
3. Lutembacher, R.: De la stenose mitrale avec communication interauriculaire, Arch. d. mal. du coeur. **9**: 237, 1916.
4. McGinn, S., and White, P. D.: Interauricular Septal Defect With Mitral Stenosis, AM. HEART J. **9**: 1, 1933.
5. Jerofejeff, P.: Offenes Foramen ovale bei Mitralstenose, Frankfurt. Ztschr. f. Path. **46**: 92, 1934.
6. Mitchell, W. G., and Bauer, J. T.: Interauricular Septal Defect Associated With Mitral Stenosis. Report of a Case, Bull. Ayer Clin. Lab., Pennsylvania Hosp. **3**: 29, 1934.
7. Kirschbaum, J. D., and Perlman, L.: Interauricular Septal Defect (Primitive Ostium Primum) Associated With Mitral Stenosis (Lutembacher's Syndrome) and Syphilitic Aortitis, Illinois M. J. **76**: 380, 1939.
8. Tinney, Jr., W. S.: Interauricular Septal Defect, Arch. Int. Med. **66**: 807, 1940.
9. Söldner, F.: Missbildungen der Vorhofscheidewand des Herzens (Ostium Primum Persistens), Munich Thesis, 1904.
10. Firket, C.: Examen anatomique d'un cas de persistance due trou ovale de Botal, avec lesions valvulaires considerables du coeur gauche, chez une femme de 74 aus, Ann. Soc. méd-chir. de Liége, p. 188, 1880.
11. Sailer, S.: Mitral Stenosis With Interauricular Insufficiency, Am. J. Path. **12**: 259, 1936.
12. Arey, L. B.: Developmental Anatomy. A Text Book and Laboratory Manual of Embryology, ed. 4. Philadelphia and London, 1940, W. B. Saunders Co.
13. Dressler, W., and Roesler, H.: Vorhofseptumdefekt kombiniert mit Mitralstenose und aurikularen Leberpuls, Ztschr. f. klin. Med. **112**: 412, 1930.
14. Abbott, M. E.: Atlas of Congenital Heart Disease, New York, 1936, Am. Heart Assoc.
15. Roesler, H.: Interatrial Septal Defects, Arch. Int. Med. **54**: 339, 1934.
16. Assmann, H.: Klinische Röntgendiagnostik der inneren Erkrankungen, ed. 4, Leipzig, 1928, F. C. W. Vogel, page 89.
17. Straub, H.: in Bethe, A., and Bergmann, G.: Handbuch der normalen und pathologischen Physiologie, Berlin, 1926, Julius Springer **7**: page 239.
18. Curtis, A. H.: Obstetrics and Gynecology, Philadelphia and London, 1933, W. B. Saunders Co., Vol. 1.
19. Gross, L.: Blood Supply to the Heart, New York, 1921, Paul B. Hoeber Co.
20. Müller, W.: Die Massenverhältnisse des menschlichen Herzens, Voss, Hamburg and Leipzig, 1883.
21. Morris' Human Anatomy, edited by C. M. Jackson, ed. 9, Philadelphia, 1933, P. Blakiston's Son & Co.
22. Fetterolf, G., and Gittings, J. C.: Some Anatomic Features of the Child's Thorax and Their Practical Application in Physical Diagnosis, Am. J. Dis. Child. **1**: 6, 1911.
23. Abt's Pediatrics, Vol. 4, Philadelphia and London, 1924, W. B. Saunders Co.
24. Wahl, H. R., and Gard, R. L.: Aneurism of the Pulmonary Artery, Surg., Gynec., & Obst. **52**: 1129, 1931.

THE EFFECT OF CHRONIC LEAD POISONING ON ARTERIAL BLOOD PRESSURE IN DOGS

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THE belief that chronic lead poisoning leads to arterial hypertension extends deep into the annals of clinical medicine, but the evidence on which it is based is unconvincing. Lead intoxication has been studied in a number of animal species, but rarely has the blood pressure been measured, and then the method employed has not been the best.

Since little is known of the effect of lead intoxication on arterial blood pressure, we thought it desirable to make a prolonged study of the effect on mean arterial pressure of feeding two dogs diets in which the amount of lead was accurately measured.

METHODS

Arterial pressure was measured by direct femoral arterial puncture with a 20-gauge needle and a recording mercury manometer. Weekly erythrocyte and leucocyte counts and hemoglobin and urinary protein determinations were made. The lead, in the form of aqueous lead acetate solution, was administered by means of a short esophageal tube. The amount was calculated as metallic lead. The diet consisted of dog biscuits.

PROTOCOLS

A one-year-old female dog, weighing 9.3 kilograms, began receiving lead acetate December 31, 1937. The erythrocyte count was 7.19 millions, the hemoglobin, 111 per cent, and the leucocyte count, 15,000 (Fig. 1). The amount of lead was gradually increased until loss of appetite and weight, bloody diarrhea, and a lead line developed. It was then discontinued for a week or more until the acute symptoms and signs receded. It was necessary to discontinue lead administration on four occasions.

It is of interest that, during these four attacks of acute lead poisoning, anemia did not develop nor did an increase in reticulocytes occur. Progressively greater amounts of lead were required to produce each succeeding acute attack. After 34 months of lead administration the dog weighed 8.5 kilograms, the erythrocyte count was 6.9 millions, and the hemoglobin was 95 per cent.

Evidence of irritation of the kidneys was not found. At no time did the urine contain abnormal amounts of protein. Since the blood pressure was normal after 34 months of lead administration, it seemed desirable to try to elevate the pressure by removing normal renal tissue. Unilateral nephrectomy was therefore performed, but still no rise in pressure occurred. A rapid decrease in weight was observed, and 27 days later severe lead poisoning developed. Marked encephalitis accompanied this attack. The dog was in such poor condition that she was sacrificed on December 31, 1940. During the final illness the erythrocyte count decreased to 5.97

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millions and the hemoglobin to 60 per cent; this was associated with a rise of reticulocytes to 6.2 per cent on the day of death. There had been no reticulocytosis prior to the final attack. This suggests that the variations in the erythrocyte count resulted from differences in hydration of the dog, rather than alterations in production and destruction. Autopsy showed the usual morbid changes which are induced by lead intoxication.

This dog received a total of 32.5 grams of lead over a period of three years.

A second dog was studied for a much shorter time because it died during the second attack of acute lead poisoning after a total of 1.9 grams of lead had been administered. No abnormal changes in arterial pressure were observed.

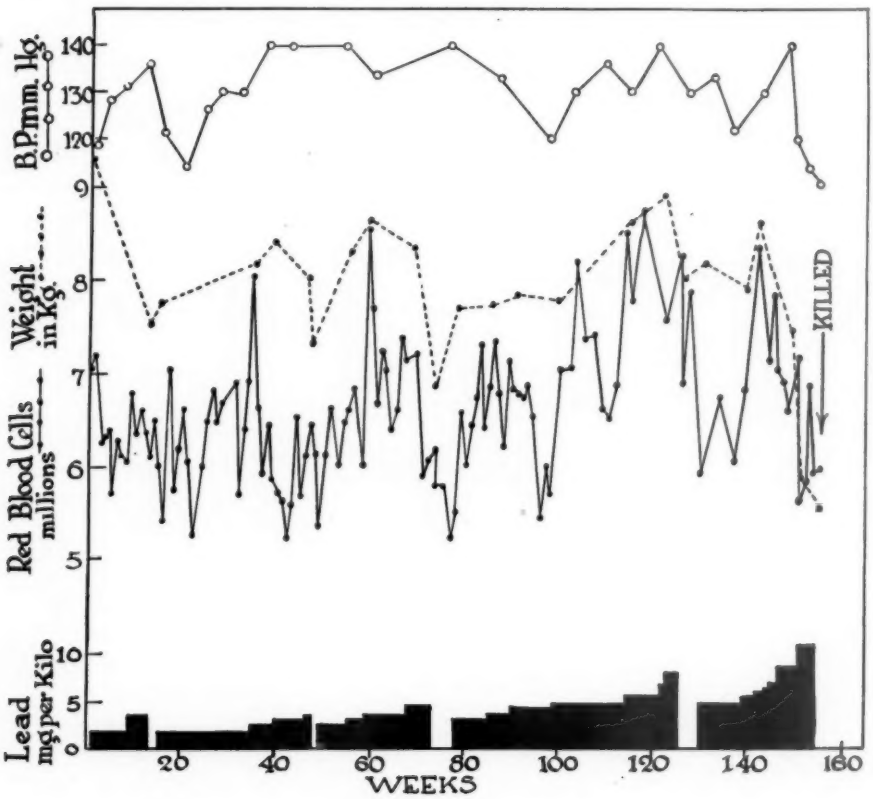

Fig. 1.

DISCUSSION

Despite prolonged (160 weeks) administration of large amounts (32.5 grams) of lead to a dog, no significant change in mean arterial pressure occurred. The dog survived four attacks of acute lead poisoning and died during the fifth, indicating the severity of the treatment. Weight loss and bloody diarrhea occurred when the amount of lead was progressively increased; this culminated in an acute attack, but recovery soon took place when the administration of lead was discontinued. At the height of the first four acute attacks there was no demonstrable

anemia. However, there was a temporary decrease in the erythrocyte count and hemoglobin percentage after the attacks; this suggested that concentration during the attacks masked slight anemia.

Arterial hypertension can be produced in dogs with ease by other methods, and therefore there is no reason to suppose that it would not occur after lead administration if this substance were capable of producing it. Since the animal received lead in large amounts for about one-third of its life span, time for the development of hypertension was certainly adequate. We therefore conclude that lead, under the experimental conditions which were used by us, does not produce arterial hypertension in dogs.

It was stated before that careful reading of the literature on the possible relationship between chronic lead poisoning and hypertension in human beings leads to the conviction that such a relationship has not been demonstrated. The problem in human beings needs reinvestigation.

CONCLUSION

Administering lead to dogs over long periods of time and in large amounts does not produce arterial hypertension.

THE SEGMENTAL AND AGEING VARIATIONS OF REACTIVE HYPEREMIA IN HUMAN SKIN*

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THAT the ability of the skin to undergo reactive hyperemia varies at different segmental levels has been a common observation.[1, 2] With the advent of a simple, reliable method which is capable of quantitating the threshold of reactive hyperemia to local ischemia, it is now possible to map by serial segments the capacity of the skin to respond in this regard.[3] Furthermore, data obtained upon selected subjects in proper age groups should reveal significant changes, if any, in the senescence of the smaller blood vessels of the skin.

Such a study, showing topographic and age variations of reactive hyperemia in the skin, ought to be of theoretical interest and practical importance. It should reveal the relationship between the responsiveness of the smallest blood vessels and the concentration of oxygenated and reduced hemoglobin in different cutaneous body segments, as recently measured by Edwards and Duntley.[4] The role of local skin temperature in the control of small dermal blood vessel responses might be further elucidated.

In practice, such data might serve as a base line of the capacity for reactive hyperemia of the small dermal vessels in different body segments. The uses of this would be many. It might aid in estimating the proper strength of drugs to be applied to the skin in various body areas; in the interpretation of the local responses in allergy testing; and as a means of comparison in the study of the smaller skin circulation in cases of organic and functional closure of blood vessels.

METHODS AND PROCEDURES

The methods used in these studies have been described previously.[3] In that paper it was shown that the reactive hyperemia which results from local ischemia produced by applying weights to the skin can be quantitated. Furthermore, the threshold hyperemia response which was obtained followed the postulates of Lewis[1] concerning the smallest blood vessels of the skin, and therefore was a measure of their responses rather than those of the arterioles. Over 500 determinations were made on about 100 subjects. It was shown that the threshold response did not vary in the same subject when it was ascertained on the same day under conditions of ordinary activity, environment, and diet. There was a seasonal change in the threshold, however, which correlated with the prevailing outside temperature. It was demonstrated that the threshold varied reliably with reflex

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heat, and with local heat and cold in a manner consonant with known concepts of blood vessel responses. The local and remote changes in the threshold consequent to acute and prolonged stasis were elucidated. It is therefore felt that the method used in this study is a reliable criterion of the hyperemia responses of the smallest dermal blood vessels of the human skin. A brief description of the technique will now suffice.

To the bottom of a 500-gram lead weight is attached a smooth rubber ring whose lower surface is five square centimeters in area. This weighted ring, which obviously has a weight loading of 100 grams per square centimeter, can be applied to practically any surface of the body. In practice the following procedure was adopted. The weight is quickly and deftly applied to the selected area of skin, and held balanced by the tip of the forefinger, exerting as little additional pressure as possible. After a certain time, measured in seconds by a stopwatch, the weight is quickly removed and the resulting reactive hyperemia is carefully observed. Various stimulation times are tried. The period of stimulation which is just sufficient to produce a hyperemic ring of even intensity and texture, with discrete edges, is known as the *threshold time*. It has been found that the average stimulation time for such a response in the skin of the forearm is about 10 to 15 seconds in midsummer and about 70 to 80 seconds in midwinter. When the stimulation time is less than threshold, a mottled, uneven ring results; when it is more than the threshold time, a more intense hyperemic ring develops, with an arteriolar flare. At the threshold, the time in seconds required for the hyperemic ring to fade to the color of the surrounding skin is taken. This is known as the *clearing time*, and is directly related to the rate of blood flow in the skin.[3] All observations are made with the aid of a blue, or daylight, mazda bulb. The environmental temperature was usually 75° F.

All the subjects for this investigation were patients on the wards of Kings County Hospital, Long Island College of Medicine Division. All were males, with the exception of subject A. D. Particular care was taken to ascertain that they were normal physically and mentally. Nearly all of them had entered the hospital for a minor elective surgical operation, such as herniorrhaphy or hemorrhoidectomy. Two subjects, H. B. and A. D., had completely recovered from a minor attack of rheumatic fever. No subject was used who had a history of skin rashes, allergic disorders, or peripheral vascular disease. Subjects in the fourth decade, or over, were tested oscillometrically for evidence of organic closure of the vessels of the extremities.

Following the recommendations of Purves-Stewart,[6] with modifications, the surface of the human body was considered as a map with no anteroposterior dimension, and the limbs were placed in a position analogous to that of the alligator (see Fig. 1). It will be observed that in this position the nerve distribution of the limbs follows the serial order of the somatic segments. This greatly facilitates vizualization and interpretation of the data.

RESULTS

Individual Gradient of Reactive Hyperemia.—The thresholds and clearing times were ascertained in fourteen dorsal and fifteen ventral positions, covering all the cutaneous branches of nerve segments from the ophthalmic division of the fifth cranial nerve to the fifth sacral nerve (Fig. 1). Despite individual variations, certain definite trends were found in the trunk of a normal person in the third decade of life.*

*In this investigation, seasonal changes in reactive hyperemia in the skin, as previously demonstrated, do not enter as a significant factor,[3] since practically all the subjects were studied at the same time of the year, namely, September and October, 1941.

TABLE

THE SEGMENTAL THRESHOLDS AND CLEARING TIMES OF FOURTEEN REPRESENTATIVE SUBJECTS, THE MOST MARKED CHANGES ARE

REGION OF BODY	B. S. Age=2		A. D. Age=9		D. Z. Age=12		H. B. Age=13		D. G. Age=24		L. S. Age=26		A. M. Age=29	
	Th.*	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.
FACE														
Forehead	15	45	15	40	15	20	20	30	13	23	23	40	13	25
Cheek	28	40	18	33	13	30	15	27	18	27	8	20	33	43
NECK														
Dorsal	30	31	28	40	23	38	13	19	15	30	23	35	35	30
Ventral			20	25	35	40	25	25	40	25	15	50		
TRUNK														
Dorsal														
Scapular	30	31	28	30	38	35	23	25	43	40	23	50	38	35
Lower chest	33	38	28	25	33	20	25	30	48	50	23	25	33	28
Lumbar	25	30	30	23	33	25	28	30	48	20	28	30	33	18
Buttocks	13	14	18	15	12	12	13	15	23	20	18	20	13	18
Ventral														
Upper chest	35	23	30	110	28	45	55	55	58	28	38	50	35	30
Lower chest	35	23	35	105	48	29	45	35	68	38	28	33	30	25
Upper abdomen	38	68	40	25	55	70	45	35	70	30	33	25	35	25
Lower abdomen	38	95	33	15			45	35	70	30	40	25	40	26
UPPER EXTREMITY														
Dorsal														
Axillary (Deltoid)	25	25	30	25	35	50			20	20	30	75	28	33
Brachium	28	28	33	45	48	65	25	35	70	55	35	85	40	30
Antibrachium	33	60	38	73	43	45	35	40	73		58		43	35
Hand	33	40	33	80	35	60	18	36	63	80	58	70	43	40
Ventral														
Brachium	33	32	33	83	45	70	45	43	63	90	38	80	48	45
Antibrachium	33	42	38	40	45	70	38	40	63	80	58	78	43	45
Palm	28	28	28	30	38	60	25	40	28	50	38	55	33	28
LOWER EXTREMITY														
Dorsal														
Upper thigh			40	70	60	65					53	55		
Lower thigh	33	52	48	85	60	65	50	43			78	90	120	90
Upper leg	38	54	45	48	73	87	60	25			98	95	120	110
Lower leg			55	93	70	140	90	65			128	130	110	250
Foot	35	95	70	100	80	160	110	80	120	225	110	600	85	110
Ventral														
Upper thigh	33	88			45	50			75	55	73	120		
Lower thigh					38	35	50	32	85	80	78	150	78	60
Upper leg	28	49			63	73	55	53	93	60	80	220	165	160
Lower leg					58	55	80	32	120	140	115	200	175	200
Sole (Plantar)	25	50	38	70	45	45	28	36	70	55	50	480	60	94

*Th. = threshold time in seconds.
C.T. = clearing time in seconds.

I

SHOWING THE EFFECTS OF ADVANCING AGE UPON THE SEGMENTAL GRADIENTS. NOTE THAT LIMITED TO THE LOWER EXTREMITIES

P. B. Age=30		T. S. Age=42		L. E. Age=47		A. Mac. Age=51		D. R. Age=51		V. C. Age=72		W. W. Age=80	
Th.	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.	Th.	C.T.
43	55	23	55	35	60	38	60	18	25	13	25	18	28
43	65	30	42	35	86	38	60	23	50	15	25	110	75
48	60	75	95	35	60	68	85	40	45	43	30	63	35
30	37	28	40			38	50	25	62	23	23	48	40
38	35	65	110	55	70	65	125	43	45	40	35	28	25
40	23	60	75	45	70	65	135	38	35	45	38	38	35
40	20	50	30	75	85	58	35	48	30	30	20	43	32
28	13	28	25	35	43			38	20	25	13	9	20
60	80	63	110	45	90	70	42	48	51	48	35	28	45
40	32	65	100	35	75	60	95	48	47	48	45	23	35
50	20	55	180	35	40	73	22	65	60	48	25	23	31
48	22	55	180	35	40			80	75	48	25	23	31
		55	115	40	41	55	70	45	45	48	30	43	35
		55	100	80	95	70	105	53	53	50	40	40	45
43	40	68	70	85	100	58	120	100	105	98	75	33	40
50		60	90	120	155	68	100	110	110	58	90	38	48
38	66	48	100	38	104	68	100	48	90	73	65	48	72
38	66	43	100	38	110	50	75	63	100	75	80	43	45
40	80	35	48	100	120	58	120	38	55	50	55	38	20
45	75	75	90	100	125			55	55	83	100	73	65
60	30	65	135	100	125	180	120	75	85	83	105	68	50
55	40	95	170	110	105	145	145	110	200	93	75	240	300
70	100	85	195	110	130	110	350	100	300	98	90	300	420
83	120	85	180	90	95	110	250	100	600+	105	200	300	600+
55	80	103	115	100	119	120	125	50	40			68	25
33	25	83	125	100	122	135	110	75	75			63	40
58	70	110	130	100	130	240	150	110	200	105	180	300	300
58	80	110		80	107	180	180	120	240	105	330	240	300
28	100	55	75	100	100	50	100	110	300	48	45		

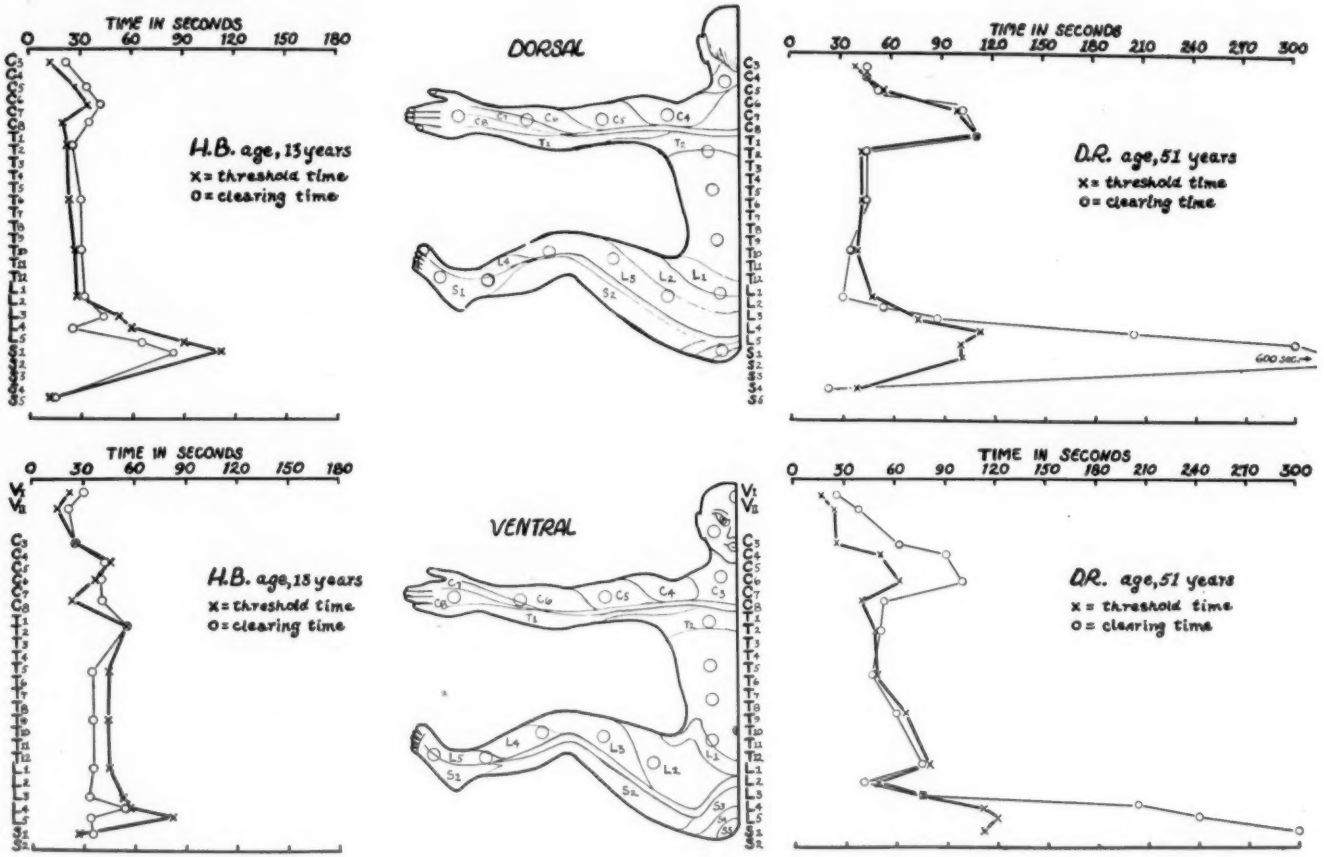
TIME IN SECONDS
0 30 60 90 120 150 180
H.B. age, 13 years
X = threshold time
O = clearing time
DORSAL
TIME IN SECONDS
0 30 60 90 120 150 180 210 240 270 300
D.R. age, 51 years
X = threshold time
O = clearing time
600 sec.
TIME IN SECONDS
0 30 60 90 120 150 180
H.B. age, 13 years
X = threshold time
O = clearing time
VENTRAL
TIME IN SECONDS
0 30 60 90 120 150 180 210 240 270 300
D.R. age, 51 years
X = threshold time
O = clearing time

Fig. 1.—Relationship of various nerve segments and their respective thresholds (crosses) and clearing times (circles). Both dorsal and ventral gradients are illustrated in a subject in the second decade and one in the sixth decade of life. The circles on the figures correspond approximately to the areas of application of the weighted ring.

It was found that there is a slight but constant positive gradient in the thresholds and clearing times as one passes from the highest to the lowest nerve segments. Thus, in subject A. M. (Table I) the threshold in the flush areas of the body (face, neck, and upper part of the chest) was about 33 seconds; over the lower part of the abdomen it rose to 40 seconds. The clearing times closely parallel the threshold times. Close scrutiny of Table I and Fig. 1 will reveal that the gradient in the trunk is generally more marked on the ventral surface. One constant feature in all subjects was a very low threshold over the buttocks (sacral 4-5), which compared favorably with the most reactive parts of the body, such as the face and neck.

In the extremities, as might be expected, there is a very marked gradient in thresholds and clearing times. Thus, in subject A. M. (Table I) the threshold for the ventral surface of the forearm was 43 seconds and the clearing time was 35 seconds, whereas, on the ventral surface of the lower part of the leg, the threshold was 175 seconds and the clearing time 200 seconds. The more marked rise of clearing time in this latter instance signifies that there was a slowing of the cutaneous blood flow in this region. This will be more fully discussed later. Generally, the threshold was somewhat lower and the clearing time longer in the palm and the sole, as in this subject. Variations in this respect are attributable to the thickness of the stratum corneum in this area, which interfered with the reading of the reactions.

The Variations of Threshold With Age.—By selecting 14 representative subjects, grouped roughly into decades, it was possible to study any age variations that might be present in the thresholds and clearing times. It will be seen by glancing from left to right in Table I that there are no significant ageing differences in so far as the flush areas of the body or the trunk itself are concerned. In the extremities, however, there is a gradually increasing threshold, and this is directly related to age. This is most marked and constant in the lower extremities. Thus, in subject W. W., who was an unusually hale and hearty person of eighty years, whose habit it was to walk two miles each day, the threshold showed a remarkable rise to 300 seconds and the clearing time to 600 seconds in the foot. Study of Table I reveals that this rise in the lower extremities is constant in persons in the second decade of life or older. Furthermore, with some exceptions, the rise in threshold seems to be roughly proportional to the age of the subject. The even greater rise of clearing time in this area, it may be noted, betokens a local slowing of blood flow. Another striking feature of the results was the absence of a gradient in the youngest subjects, B. S. and A. D. (Fig. 2 and Table I). This was particularly pronounced in the former. During the actual course of the determinations there was little difference in the reactions, either qualitatively or quantitatively, no matter which area of the body was studied. This is in marked

contrast to older subjects, in whom gross differences are immediately apparent when one passes from the trunk to the extremities.

Although the number of subjects in each age group is small, it must be remembered that each subject was carefully selected and had a

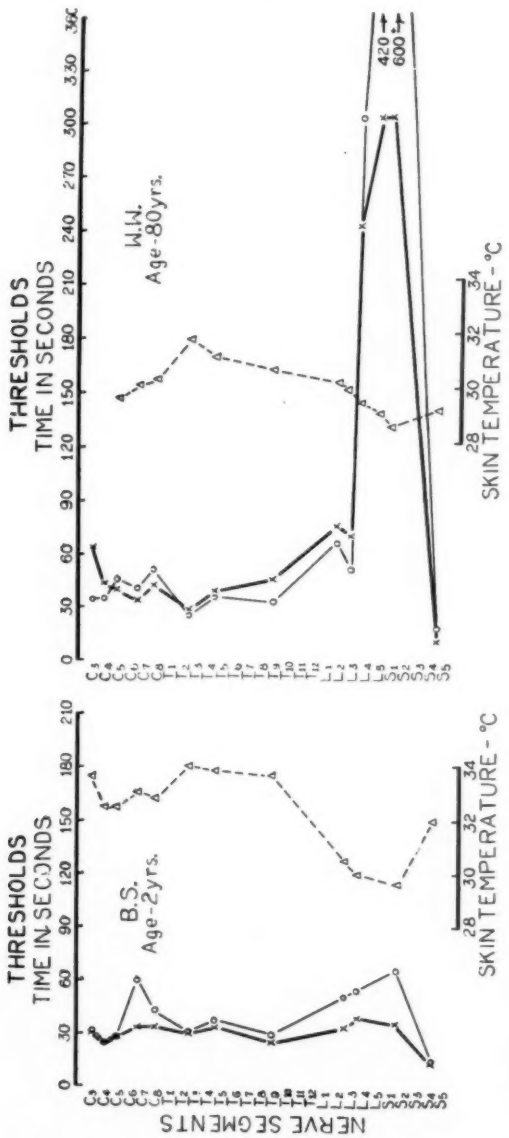

Fig. 2.—Comparison of the gradients of thresholds (crosses) and clearing times (circles) to the corresponding surface temperature gradients (triangles) in a subject in the first decade and one in the ninth decade of life. Only the dorsal surface has been plotted in this diagram. See text for discussion.

total of 29 separate serial determinations of the threshold of reactive hyperemia. Moreover, the fact that the responses in the lower extremities vary with age, whereas those in the face and trunk do not, lends support to the view that the ageing variations which were observed

are actual ones. To narrow the limits of this ageing difference, a study on a much larger group of subjects is contemplated, but restricted to fewer and significant segmental areas.

Surface Temperature and the Segmental Threshold.—In over two-thirds of the subjects, surface temperatures were taken in each area in which the threshold was studied.* Thus, the segmental gradient of surface temperatures could be compared to the segmental threshold. Fig. 2 shows the segmental thresholds and surface temperatures in the youngest and oldest members of the series. It will be seen that there is no exact correlation. In the extremities, as is to be expected, the temperatures are lowest, and it is here that the highest thresholds and clearing times are obtained. The relationship is by no means a linear one, however, especially in the younger subjects. This is surprising, for our own previous studies and those of other investigators have demonstrated that changes in temperature, not only local, but also reflex and environmental, have profound effects upon blood flow and reactive hyperemia in the skin.[3, 7, 8, 9] There are other factors, however, which must be taken into consideration. The techniques of recording surface temperatures are by no means perfect. The temperatures we obtained agree in general with those of other investigators,[5, 7] but their studies were unfortunately limited to one age group, usually adults in the third decade of life. Our studies include the very young and the very old, and it is at these ages that the most divergent results are found.

It must also be stressed (as has been pointed out before[3, 10]) that these vascular reactions are localized to the smallest blood vessels of the skin; namely, the vessels beyond the arterioles. Factors which may ordinarily have demonstrable effects upon the larger vessels may not as markedly influence the responses of these smallest vessels. It is also probable that factors other than temperature are just as important in the local control of the smallest blood vessels.[1, 3, 10]

The main purpose of the temperature studies reported here is served, however. That is to demonstrate that in different subjects the segmental gradient of reactive hyperemia is not necessarily dependent upon the segmental gradient of surface temperatures. This is clearly demonstrated in Fig. 2. The temperatures also served as an indication that the subject was under standard conditions of arterial tone, and not under an unusual degree of vasoconstriction or vasodilation.

Local Blood Flow and the Segmental Threshold.—The rise of thresholds in the lower extremities requires further explanation. The thought which comes immediately to mind is that the most salient factor in the segmental gradient of reactive hyperemia is local blood flow in the skin.

*A Tycos Dermatherm was used in some of these determinations, and a Leeds and Northrup Automatic Recording Micromax, with a 30-gauge iron-constantan junction, was used in the rest. Care was taken to secure optimal conditions for the recording of surface temperatures. The room temperature was maintained at 75° F., and the subject, who was lightly clad, was left exposed to room air for one hour.

Repeated observations have shown that dilation of small blood vessels may be elicited even when there is complete stasis in an extremity.[1] It has also been demonstrated that the threshold of reactive hyperemia to local ischemia is not changed by complete stasis, but that the clearing time is very markedly prolonged.[3] This is ascribed to the fact that blood flow is essential for removal of the hypothetical "H" substance which is produced by the ischemia.

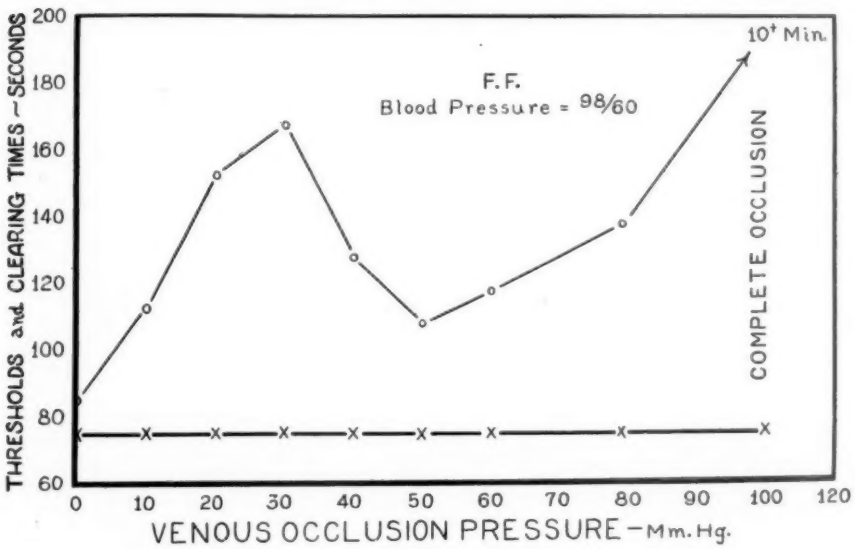

Fig. 3.—Effects of gradually increasing venous occlusion upon the thresholds (crosses) and the clearing times (circles), as ascertained on the skin of the ventral surface of the forearm.

In order to test these observations further, the following experiment was performed several times. Using the skin of the ventral surface of the forearm, the thresholds and clearing times were obtained. By means of a blood pressure apparatus, venous stasis was then produced, and the thresholds and clearing times again determined. This was done at intervals of 10 mm. Hg until complete stasis was attained. Ample time was allowed after determination at a certain pressure to insure complete circulatory recovery of the limb. The results of one such experiment are charted in Fig. 3. There was no change in the threshold time, as was expected. The clearing time, however, rose rapidly to 167 seconds at 30 mm. Hg occlusion pressure. Beyond this pressure there occurred a shortening of clearing time which reached its lowest point, in this instance, at 50 mm. Hg. This point was considerably above the control clearing time. As the occlusion pressure was further increased there was a gradual rise in the clearing time, until, with complete circulatory stasis, the time for the hyperemic rings to clear became infinitely long. It was observed for 10 minutes

in this instance, at which time the hyperemic area was still very pronounced. Presumably the secondary fall in clearing time at 30 mm. Hg was the result of dilation of vessels on the arterial side as part of the mechanism of compensation for the venous stasis. This explanation is supported by the observation of Lewis and Grant[11] that *during* the period of venous stasis in a limb the arterial pulse, as recorded by a plethysmograph, increases in volume. It is notable that the clearing time during this secondary fall does not descend to the control level, and therefore blood flow in the smallest skin vessels *during* venous stasis only approaches the normal resting blood flow, and does not exceed it. The contention of Linton, et al.,[12] that the arterial inflow in a limb in which venous obstruction is present actually exceeds the normal resting inflow is therefore not confirmed by these studies.

It seems, therefore, that the long clearing times in the extremities of the aged are the result of a local slowing of blood flow. The high thresholds observed in the same regions cannot be ascribed to this cause, however. Other factors, i.e., nervous, postural, and humoral, undoubtedly contribute to this effect.

DISCUSSION

Anatomic studies of the segmental and age variations in the smallest blood vessels of the skin have been made, but unfortunately they have not included the lower extremities. It has been found that the number of capillaries in the cheek, ear lobe, forearm, and hand does not differ significantly.[2] In addition, there are no discernible changes with advancing age.[13] Our studies on the functional responses of these small blood vessels confirm these observations. They add the fact, however, that the most marked gradient is in the lowest nerve segments, and, furthermore, that the ageing effects occur almost exclusively in the lower extremities. Wetzel and Zotterman[2] also showed that the highly colored regions of the body, such as the cheek, owe this property to a relatively atonic state of the capillaries and venules. It is therefore reasonable to assume that segmental threshold differences in the responses of these small vessels are the result of functional alterations, rather than anatomic ones. A morphologic study of the capillaries in the lower extremities with respect to ageing would be desirable, however.

The excellent studies of Edwards and Duntley[4] have demonstrated that the ratio of reduced to oxygenated hemoglobin, as ascertained by spectrophotometric analysis of the skin, may vary markedly. The proportion of oxyhemoglobin is highest in the cheek, palm, buttocks, and sole, and increased in the face and upper part of the chest; that of reduced hemoglobin is greatest in the lower part of the abdomen, scrotum, and dorsum of the foot. It is, therefore, obvious from our

studies that the most responsive skin areas correspond closely to the regions which are most rich in oxyhemoglobin, and vice versa. It has also been demonstrated that the sensitivity of the smallest blood vessels is markedly decreased in systemic anoxemia before there are marked changes in blood pressure, pulse rate, and respiratory exchange.[10] The implication is that one of the most important factors which determine the reactivity of these vessels is the degree of oxygenation of the blood they contain.

It is generally maintained (and Abramson, et al.,[14] have recently confirmed this by plethysmographic studies of various portions of the extremities) that the degree of the hyperemic response consequent to deprivation of blood is related to the metabolic needs of the tissues concerned. Also, it is well known that the skin, particularly that of the hand and foot, serves the important function of dissipating heat. Sheard and Williams[7] have demonstrated that the basal metabolic rate of normal persons is related to the temperature fall in the toes when the extremities are left exposed under standard environmental conditions. Those with the higher basal metabolic rates showed the least temperature fall.

These studies, however, were carried out with methods which measure largely the responses of arterioles (plethysmographic and surface temperature); consequently, the results may not apply directly to the responses of the smallest blood vessels which we have studied. With this difference in mind, certain correlations are indicated. Those areas of the body which are most subject to pressure, and contact with the atmosphere, i.e., the palms, soles, buttocks, cheeks, and therefore incur the greatest metabolic debt, have the most responsive blood vessels and are supplied with the most highly oxygenated blood. On the other hand, the skin of the lower extremities, with the exception of the sole, because of its location, is seldom called upon to bear the weight of the body, either in the erect or the recumbent posture. The surface temperature in these regions is also consistently lower than that of the rest of the body, and it is here that the highest thresholds of the reactive hyperemia which results from local ischemia are found.

SUMMARY AND CONCLUSIONS

By using a method which was previously developed for quantitating the reactive hyperemia which results from local ischemia, it was possible to study this response in serial body segments. Two components are described, namely, a *threshold* and a *clearing time*. Correlations were made with surface temperatures and with age. The following conclusions were reached:

1. There is a positive gradient of reactive hyperemia resulting from local ischemia which is directly related to the nerve segment involved.

The more caudal the nerve segment, the higher the threshold and clearing time. This gradient is slightly more marked on the ventral surface of the body.

2. Certain areas of the body are more responsive than the mean gradient. These include the palm, sole, cheek, and buttocks.

3. The extremities cause sharp peaks in the mean slope of the gradient. This sharp rise in threshold and clearing time is much more marked in the lower extremities.

4. In general, the clearing time, which has been shown to be directly related to blood flow, parallels closely the threshold time. In the lower extremities, however, it may rise to much greater levels than the threshold.

5. Simultaneously conducted segmental temperature studies indicate that, under standard environmental conditions, the segmental gradient of temperature is not the principal factor in the difference in the segmental gradients of reactive hyperemia which are observed in different subjects.

6. With advancing age, the slope of the gradient of the thresholds becomes more inclined. The youngest subjects may show no gradient at all, whereas the most aged show a very steep gradient. This phenomenon is limited largely to the lower extremities. In this regard, age affects the clearing time even more. This is attributed to a normal, marked slowing of local cutaneous blood flow in the extremities of the aged.

7. These observations suggest that any studies on reactive hyperemia in the skin, either in health or in disease, in order to be well founded, must be interpreted in the light of what segmental areas are studied and the ages of the subjects.

REFERENCES

1. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, 1927, Shaw & Sons, Ltd.
2. Wetzel, N. C., and Zotterman, Y.: On Differences in the Vascular Colouration of Various Regions of the Normal Human Skin, Heart **13**: 357, 1926.
3. DiPalma, J. R., Reynolds, S. R. M., and Foster, F. I.: Quantitative Measurement of Reactive Hyperemia in Human Skin: Individual and Seasonal Variations, AM. HEART J. **23**: 377, 1942.
4. Edwards, A. E., and Duntley, S. Q.: The Pigments and Color of Living Human Skin, Am. J. Anat. **65**: 1, 1939.
5. Fay, T., and Henry, G. C.: Correlation of Body Segmental Temperature and Its Relation to the Location of Carcinomatous Metastasis; Clinical Observation and Responses to Methods of Refrigeration, Surg., Gynec. & Obst. **66**: 512, 1938.
6. Purves-Stewart, J.: The Diagnosis of Nervous Diseases, ed. 8, Baltimore, 1937, William Wood & Co.
7. Sheard, C., and Williams, M. M. D.: Skin Temperatures of the Extremities and Basal Metabolic Rates in Individuals Having Normal Circulation, Proc. Staff Meet. Mayo Clin. **15**: 758-762, 1940.
8. Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and Sympathectomized Hand, Am. J. Physiol. **113**: 384, 1935.
9. Brown, G. E., and Allen, E. V.: Continuous Vasodilatation in the Extremities Produced Reflexly: Physiologic Studies on Temperature of Skin and on Volume Flow of Blood, AM. HEART J. **21**: 564, 1941.

10. DiPalma, J. R., Reynolds, S. R. M., and Foster, F. I.: Measurement of the Sensitivity of the Smallest Blood Vessels of the Human Skin: Responses to Graded Mechanical Stimulation in Normal Men, J. Clin. Investigation **20:** 333, 1941.
11. Lewis, T., and Grant, R.: Observations Upon Reactive Hyperemia in Man, Heart **12:** 73, 1925.
12. Linton, R. R., Morrison, P. S., Ulfelder, A., and Libby, A. L.: Therapeutic Venous Occlusion: Its Effect on the Arterial Inflow to an Extremity as Measured by Means of the Rein Thermostromuhr, AM. HEART J. **21:** 721, 1941.
13. Weiss, S., and Frazier, W. R.: The Density of the Surface Capillary Bed in the Forearm in Health, Arterial Hypertension and in Arteriosclerosis, AM. HEART J. **5:** 511, 1930.
14. Abramson, D. I., Katzenstein, K. H., and Ferris, E. B.: Observations on Reactive Hyperemia in Various Portions of the Extremities, AM. HEART J. **22:** 329, 1941.

A REACTIVE HYPEREMIA RING TEST IN THE STUDY, EVALUATION, AND PROGNOSIS OF PEDAL LESIONS CAUSED BY ARTERIOSCLEROSIS OBLITERANS AND ARTERIAL EMBOLISM*

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THE immediate object of this investigation was to apply a direct quantitative method, recently developed and studied,[1, 2] to the evaluation of the skin circulation in obliterative vascular disorders. Kramer and others[3, 4] have stressed the importance of such studies in peripheral vascular disease, as contrasted to the usual means of evaluating the functional capacity of the larger arteries, such as oscillometry, plethysmographic and roentgenologic studies.

Existing methods which were devised to achieve this are the histamine test, advocated by Starr,[5] and the intradermal saline wheal test of McClure and Aldrich.[6] In our experience and that of others,[3, 4] the histamine wheal test is an efficient and quick means of obtaining a rough idea of the functional capacity of the smaller skin vessels. It frequently falls far short of exact quantitation, however, and suffers from certain other disadvantages. For example, we have noted that people vary in sensitivity to histamine, and, further, that the most intense responses, although delayed, develop in the presence of a greatly diminished dermal blood flow. In addition, this test depends upon the formation of a wheal; this response is not easily reversible, and therefore borders more on the pathologic than on the physiologic. The inherent disadvantages of the intradermal saline wheal test are discussed elsewhere.[3, 4]

The method used in the experiments to be described has been shown to be a simple, sensitive, and accurate means of quantitating the responses of the smallest vessels of the skin to local circulatory stasis. It requires nothing more in the way of apparatus than a weighted rubber ring, a stop watch, and a daylight Mazda bulb. Individual, seasonal, segmental, and ageing variations have been described. This procedure measures the ability of the smallest blood vessels of the skin to respond by reactive hyperemia to local ischemia, and, by noting the time required for the area to clear, a direct indication of the rate of local blood flow is obtained.[1, 2]

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The results of such an investigation upon a selected group of patients who had been adequately studied by the usual methods of examination in peripheral vascular disorders should yield information on at least three points. First, it might serve to indicate whether or not the loss of function of the blood vessels in the skin is the result of a change in the capacity of the smallest blood vessels to respond by reactive hyperemia to local ischemia. Second, it might clarify the exact relationship between obliteration of large vascular trunks and slowing of dermal blood flow. Third, it might serve to provide an exact measure of the degree of functional loss of the skin circulation.

METHOD AND PROCEDURES

Upon the morning of examination the patient was asked to rest in bed in the horizontal position for one hour. He was lightly clad and the room temperature was maintained at about 75° F. After a careful history, physical examination with reference to peripheral vascular disease was begun. Careful note of the physical qualities of the skin and nails was made. The presence or absence of the pulses and their strength and volume were ascertained by palpation. A modified Buerger's test[4, 7] was then done, as follows: The patient's lower extremities were elevated so that the feet were about 18 inches above the level of the heart. He then dorsiflexed and extended his foot about once a second, moving his toes at the same time. The time required for pallor to appear in any part of the foot was then noted. Finally, the patient was asked to hang his feet over the side of the bed in order to ascertain whether rubor would develop. This completed the usual clinical examination.

The laboratory procedures were kept as standard as possible. Oscillometric readings were made by the same person, with the same instrument, throughout. A histamine test was done on nearly every patient, using the technique described by de Takáts,[8] and the results were recorded according to the recommendations of Kramer.[3] A modified Landis-Gibbon test[9] was done on those patients who seemed to have more symptoms than the degree of their organic occlusion indicated. This was performed as follows: Skin temperatures were taken on the big toe, dorsum of the foot, ankle, mid-leg, and thigh. Short wave diathermy was then applied to the region of the lower part of the spine for 30 minutes, and skin temperatures again taken 15 minutes after the cessation of this treatment.[10] In our experience, this method of securing reflex vasodilation is not as effective as immersing the hands in warm water as originally recommended by Landis and Gibbon. However, the former method is very convenient, and the results are sufficiently exact for the purpose of this investigation.*

The reactive hyperemia ring test was usually done on the day after the above examination, in order to obviate differences which might be caused by the histamine flares. Four areas, corresponding to the usual areas of injection of histamine[3] on each limb, were studied. These areas were the lateral aspect of the thigh, just above the knee (L3), the lateral aspect of the leg, just below the knee (L4), the lateral aspect of the ankle (L4, 5), and the dorsum of the foot (L5, S1). These sites also correspond exactly to the areas which were studied previously in ascertaining the segmental gradient of reactive hyperemia in the lower extremities.[2] This was done so that any abnormal results could be compared to the expected normal gradient in the proper age group. The time needed to make a complete study of both extremities was greatly shortened by the simple expedient of using two, or even three, weights and stop watches, so that several areas could be studied simultaneously.

*Dr. John J. Hauff was most kind in permitting us to use the facilities of the Department of Physiotherapy, Kings County Hospital, for the testing and examination of the patients.

RESULTS

The Type of Patients Studied.—All of the patients whom we studied were thought to have *arteriosclerosis obliterans* of the lower extremities.† In all, 24 representative patients (9 females and 15 males) were subjected to the above-mentioned tests. Of these, 6 females and 9 males were also diabetic. All of the symptoms caused by progressive, obliterative, arterial disease of the lower extremities, from the early incipient lesions to persistent infection, ulceration, and gangrene, were represented.

In Table I these patients are listed, in so far as possible, in the order of increasing degree of obliteration of the vessels of the extremities. This was judged not only by the results of the objective tests, but also by the symptomatology and the extent of the lesions which were present at the time of examination. Inciting and contributory causes had to be considered carefully. Thus, S. S., the first female patient in Table I, had, by all objective methods of study, the most adequate circulation of the group, but she presented one of the most severe pedal lesions, namely, cellulitis of the foot. However, when cognizance was taken of the inciting cause (the removal of an ingrown toe nail) this discrepancy was explained.

Comparison of Oscillometric and Thermometric Readings With the Skin Tests.—As was expected, no exact relationship obtained between the functional capacity of the larger vessels, as measured oscillometrically, and that of the smallest blood vessels, i.e., the capillaries, venules, and small arterioles, as measured in this study. Although the oscillometric reading usually indicates the side on which the arterial lesion is most advanced, it does not give an exact measure of the extent of the functional loss. Several examples of this are listed in Table I. Particularly illustrative are cases R. R. and P. G.; both patients had markedly diminished oscillometric pulsations of the same order, but the former had pregangrenous lesions, whereas the latter had minimal symptoms and lesions. This confirms the observations of many investigators;[3, 4, 8, 11] it has been attributed to the fact that the oscillometric method alone does not give any indication of the degree of arterial vasoconstriction which may exist at the time of examination. Moreover, the collateral circulation which develops after obliteration of the larger arterial trunks ordinarily does not register oscillometrically. Therefore, to obviate at least the former factor, it was considered desirable to make thermometric studies of the effects of indirect application of heat (modified Landis-Gibbon test). The results, which are summarized in Table I, show that not one of the patients had any significant degree of arterial vasoconstriction superimposed upon his vascular disease. As has been

†These patients were selected from the various services of the Long Island College of Medicine, Kings County Hospital.

TABLE

CASES OF ARTERIOSCLEROSIS OBLITERANS, SHOWING THE RELATIONSHIP OF TESTS WHICH THOSE WHICH MEASURE THE FUNCTION OF THE SKIN CIRCU

SUBJECT	AGE	OSCILLOMETRIC READINGS				HISTAMINE TEST*	SKIN TEMPERATURE
			THIGH	LEG	FOOT		
Females							
S. S. (D.M.)	58	Excellent pulsations by palpation				(R) Good in all parts. (L) Good in all parts.	(R) Increase in big toe from 29.8° C. to 31.6° C. (L) Sl. increase in big toe from 26.8° C. to 28.0° C.
I. L.	36	(R)	3¼	3¼	0	(R) Mod. delay in ft.; sl. delay in ank., leg and thigh.	(R) No change in big toe—27.0° C. to 27.3° C.
		(L)	2¼	1½	S.P.°	(L) Sl. delay in ft., ank. and leg; good in thigh.	(L) No change in big toe—27.5° C. to 27.3° C.
S. P. (R.H.D. + A.F.)	48	(R)	S.P.	0	0	(R) Sl. delay in ft. and ank.; good in leg and thigh.	(R) Increase in big toe from 27.5° C. to 29.8° C.
		(L)	½	S.P.	0	(L) Mod. delay in ft.; sl. delay in ank.; good in leg and thigh.	(L) Increase in big toe from 27.4° C. to 31.1° C.
R. S. (D.M.)	54	(R)	½	0	0	(R) Good in all parts.	(Not done)
		(L)	¾	½	⅛	(L) Sl. delay in ft.; good in all other parts.	
M. F.	74	(R)	1	0	0	(R) Marked delay in ft., ank. and leg; good in thigh.	(R) Skin temp. of big toe = 27.5° C.
		(L)	1½	3	⅛	(L) Sl. delay in ft.; good in ank., leg and thigh.	(L) Skin temp. of big toe = 30.5° C.
S. H. (D.M.)	64	(R)	1	¼	0	(R) Mod. delay in leg; sl. delay in ft. and ank.; good in thigh.	(R) Increase in big toe from 24.7° C. to 29.8° C.
		(L)	1½	¼	0	(L) Sl. delay in ft., ank. and leg; good in thigh.	(L) Sl. increase in big toe from 26.7° C. to 28.0° C.
M. K. (D.M.)	68	(R)	2	¾	0	(R) Sl. delay in ank. and leg; good in ft. and thigh.	(R) No change in big toe—30.3° C. to 30.8° C.
		(L)	1½	1¼	0	(L) Good in all parts.	(L) No change in big toe—30.2° C. to 30.8° C.
R. R. (D.M. + H.C.V.D.)	75	(R)	2	¾	S.P.	(R) Marked delay in ft.; sl. delay in ank.; good in leg and thigh.	(R) Increase in big toe from 27.5° C. to 30.5° C.
		(L)	1	⅛	0	(L) Mod. delay in ft., ank. and leg; good in thigh.	(L) No change in big toe—27.6° to 27.3° C.

*For explanation of notations of the histamine test see text.
†Th. = Threshold in seconds.
‡C. T. = Clearing time in seconds.
°S.P. = Scarcely perceptible.
D. M. = Diabetes mellitus.
A. F. = Auricular fibrillation.
R. H. D. = Rheumatic heart disease.
H. C. V. D. = Hypertensive cardiovascular disease.

I

MEASURE THE FUNCTION OF THE LARGER VESSELS (OSCILLOMETRY AND THERMOMETRY), AND LATION (HISTAMINE AND REACTIVE HYPEREMIA RING TESTS).

REACTIVE HYPEREMIA RING TEST									PERIOD OF SYMPTOMS	LESION	THERAPY
	THIGH		LEG		ANKLE		FOOT				
	TH.†	C. T.‡	TH.	C.T.	TH.	C.T.	TH.	C.T.			
(R)	70	50	78	105	78	125	58	155	Cellulitis in left ft. following removal of ingrown toe nail 3 mo. before	Atrophy of skin and nails. Big toe of left foot is hot and red.	Ind. short wave to spine. Intermit. venous occlusion.
(L)	73	75	75	105	73	120	48	90			
(R)	78	55	68	100	63	163	83	155	Coldness of ft. for 1 yr.	Sl. dryness and scaling of skin. Pallor on elevation and sl. rubor on dependency.	Ind. short wave to spine.
(L)	70	55	68	130	68	140	78	110			
(R)	50	75	68	130	85	145	110	200	Acute onset of pain in rt. ft. for 2 wk.	Scaly skin. Pallor in rt. ft. on elevation.	Ind. short wave to spine. Papaverine.
(L)	58	63	63	130	73	155	98	135			
(R)	58	80	58	80	68	220	78	200	Pain in left calf for 5 mo.	Pallor on elevation and rubor on dependency.	Discharged.
(L)	63	80	75	145	98	250	118	275			
(R)	68	18	100	80	100	1800+	65	420	Pain and swelling of rt. ft. for 1 yr.	Red, swollen rt. big toe with sl. ulceration. Atrophy of rt. leg muscle.	Referred to surgery.
(L)	68	40	85	80	95	570	115	180			
(R)	75	65	75	90	75	190	105	300	Intermittent claudication of left leg for 7 mo.	Atrophy of skin and nails.	Ind. short wave to spine.
(L)	75	55	75	100	85	300	135	900			
(R)	65	90	78	120	75	250	110	900	Nocturnal pain for 1 yr. Also intermittent claudication	Atrophy of skin and nails. Rubor of ft. at heart level.	Ind. short wave to spine. Intermit. venous occlusion.
(L)	68	70	75	145	68	600	110	840			
(R)	65	70	65	65	75	1800	110	2400	Intermittent claudication for 2 yr. infection of left heel for 2 mo.	Cellulitis of left ft.	Conservative treatment.
(L)	85	100	85	900	85	3000	95	2880			

TABLE I

SUBJECT	AGE	OSCILLOMETRIC READINGS				HISTAMINE TEST*	SKIN TEMPERATURE
			THIGH	LEG	FOOT		
M. P. (D.M.)	76	(Not done)				(R) Marked delay in lower ft. and ank.; sl. delay in upper ft., leg and lower thigh; good in upper thigh. (L) Amputated.	(R) No change in big toe—28.5° to 28.8° C. (L) Amputated.
Males							
A. L. (D.M.)	50	(R)	3	1¼	0	(R) Sl. delay in ft. and ank.; good in leg and thigh.	(R) No change in big toe—26.6° C. to 26.5° C.
		(L)	1	1	0	(L) Marked delay in ank.; sl. delay in ft.; good in leg and thigh.	(L) No change in big toe—26.6° C. to 26.8° C.
M. T.	62	(R)	5	7	½	(Not done)	(R) Increase in big toe from 28.5° C. to 30.5° C.
		(L)	2½	1½	⅛		(L) Increase in big toe from 24.9° C. to 29.8 C.
N. L.	63	(R)	½	S.P.	0	(R) Marked delay in ft.; mod. delay in leg; sl. delay in ank. and thigh.	(Not done)
		(L)	⅛	0	0	(L) Sl. delay in ft. and leg; good in ank. and thigh.	
J. S. (D.M.)	66	(Not done)				(R) Mod. delay in ft.; sl. delay in ank.; good in leg and thigh. (L) Good in all parts.	(R) Increase in big toe from 26.7° C. to 32.0° C. (L) Increase in big toe from 27.6° C. to 30.5° C.
P. G. (D.M.)	59	(R)	½	0	0	(R) Marked delay in ft. and ank.; Mod. delay in leg; good in thigh.	(R) Sl. increase in big toe from 28.7° C. to 29.8° C.
		(L)	¾	¾	0	(L) Marked delay in ft.; sl. delay in ank.; good in leg and thigh.	(L) Sl. increase in big toe from 29.1° C. to 29.8° C.
S. M. (D.M.)	61	(R)	¾	⅛	0	(R) Sl. delay in all parts.	(R) Increase in big toe from 28.3° C. to 30.5° C.
		(L)	5	9	0	(L) Sl. delay in all parts.	(L) Sl. increase in big toe from 30.2° C. to 31.1° C.
M. L. (D.M. + Lues)	69	(R)	6½	3	0	(R) Marked delay in ft.; sl. delay in leg; good in ank. and thigh.	(R) Skin temp. of big toe = 25.1° C.
		(L)	2½	¾	0	(L) Marked delay in ank. and leg; mod. delay in ft.; good in thigh.	(L) Skin temp. of big toe = 26.0° C.

—CONT'D

REACTIVE HYPEREMIA RING TEST†									PERIOD OF SYMPTOMS	LESION	THERAPY
THIGH		LEG		ANKLE		FOOT					
	TH.	C.T.	TH.	C.T.	TH.	C.T.	TH.	C.T.			
(R)	65	50	85	150	95	900	110	3600+	Gangrene and infection of ft. for 1 yr.	Amputation at left mid-thigh. Punched out ulcer between 3rd and 4th toes of rt. ft.	Referred to surgery.
(L)	Amputated										
(R)	68	55	78	90	78	250	95	200	Pain in left knee and calf for 1 yr.	Sl. atrophy of skin and nails. No. lesions.	Discharged.
(L)	68	80	78	165	78	900	88	270			
(R)	73	70	78	60	65	200	85	300	Intermittent claudication for 1 mo.	Atrophy of skin and nails. Patchy arteritis-endarteritis of 3 toes on left ft.	Ind. short wave to spine. Intermit. venous occlusion.
(L)	75	90	80	85	75	200	90	210			
(R)	78	55	83	200	88	780	98	240	Coldness of ft. Intermittent claudication for 10 mo.	Atrophy of skin and nails.	Ind. short wave to spine.
(L)	83	125	93	385	93	480	98	440			
(R)	75	65	88	150	120	480	75	900	Inability to use rt. leg for 4 mo. due to intense pain on walking	Healed ulcer on rt. ft. Atrophy of rt. leg; rt. ft. red and swollen.	Ind. short wave to spine. Intermit. venous occlusion.
(L)	83	100	78	100	78	900	88	200			
(R)	85	100	95	190	95	145	88	360	Intermittent claudication for 6 yr.	Sl. atrophy of skin and nails. No lesions.	Intermit. venous occlusion. Ind. short wave to spine.
(L)	75	55	98	135	95	230	98	900			
(R)	93	150	95	230	120	1200+	155	900	Intermittent claudication for 6 yr. Infection of rt. big toe for 1 yr.	Infection of rt. big toe; healed.	Ind. short wave to spine.
(L)	85	90	95	385	90	450	110	365			
(R)	70	160	70	240	70	240	95	540	Intermittent claudication for 6 mo. Pain in feet on walking.	Atrophy of skin and nails.	Ind. short wave to spine.
(L)	63	540	65	240	80	900	90	900			

TABLE I

SUBJECT	AGE	OSCILLOMETRIC READINGS				HISTAMINE TEST*	SKIN TEMPERATURE
			THIGH	LEG	FOOT		
F. D. (D.M.)	61	(R)	2	¼	S.P.	(R) Mod. delay in ank. and leg; sl. delay in ft.; good in thigh.	(R) No change in big toe—28.0° C. to 26.6° C.
		(L)	2½	¾	S.P.	(L) Mod. delay in ank. and leg; sl. delay in ft. and thigh.	(L) Increase in big toe from 25.5° C. to 27.4° C.
S. S. (D.M.)	53	(R)	1¼	1⅛	0	(R) Sl. delay in ft. and ank.; good in leg and thigh.	(R) Skin temp. of big toe = 24.1° C.
		(L)	¼	⅛	0	(L) Mod. delay in ft.; marked delay in ank.; good in leg and thigh.	(L) Skin temp. of big toe =26.6° C.
H. S.	65	(R)	8	6½	⅛	(Not done)	(R) Skin temp. of big toe = 30.5° C.
		(L)	5	½	0		(L) Skin temp. of big toe = 28.3° C.
T. S. (D.M.)	68	(R)	3	3	0	(R) Sl. delay in ft., ank. and leg; good in thigh.	(R) Sl. increase in big toe from 22.8° C. to 23.6° C.
		(L)	½	S.P.	0	(L) Mod. delay in ft. and ank.; good in leg and thigh.	(L) Sl. increase in big toe from 24.0° C. to 25.6° C.
B. S.	67	(R)	½	¼	0	(R) Marked delay in ank.; mod. delay in ft. and leg; sl. delay in thigh.	(R) Skin temp. of big toe = 28.9° C.
		(L)	1½	1	0	(L) Mod. delay in ft.; sl. delay in ank., leg and thigh.	(L) Skin temp. of big toe = 28.4° C.
M. S. (D.M.)	69	(R)	9	6	¼	(R) Sl. delay in ank. and ft.; good in leg and thigh.	(R) No change in big toe—27.4° C. to 26.1° C.
		(L)	6	3	⅛	(L) Sl. delay in ank.; good in ft., leg and thigh.	(L) No change in big toe—28.7° C. to 27.7° C.
A. W.	35	(R)	5½	9	¼	(Not done)	(R) Skin temp. of big toe = 31.4° C.
		(L)	2½	1	0		(L) Skin temp. of big toe = 31.0° C.
N. L.	74	(R)	2	0	0	(R) Marked delay from ft. up to knee; good in thigh.	(R) Sl. increase in big toe from 26.7° C. to 28.0° C.
		(L)	2½	1	0	(L) (Not done)	(L) No change in big toe—26.9° C. to 26.5° C.

—CONT'D

REACTIVE HYPEREMIA RING TEST†								PERIOD OF SYMPTOMS	LESION	THERAPY
THIGH		LEG		ANKLE		FOOT				
TH.	C.T.	TH.	C.T.	TH.	C.T.	TH.	C.T.			
(R) 85	95	95	350	68	1200+	95	1020+	Intermittent claudication for 1 yr. Nocturnal pain for 2 mo.	(R) Rose spots over dorsum of ft. (L) Gangrene of 4th and 5th toes. Secondary infection.	Amputation of left leg.
(L) 70	90	70	290	83	2400+	65	330			
(R) 68	50	70	120	73	900	88	2400	Intermittent claudication for 1 yr.	Small ulcers on both legs. Pregangrenous appearance of left big toe.	Intermit. venous occlusion. Ind. short wave to spine.
(L) 78	80	88	200	83	280	90	1800			
(R) 105	100	115	150	90	150	143	210	Intermittent claudication for 6 mo.	Atrophy of skin and nails. Marked rubor at heart level. Impending gangrene, L. ft.	Ind. short wave to spine. Intermit. venous occlusion.
(L) 110	120	120	200	95	500	140	2400+			
(R) 90	80	140	175	160	300	165	435	Intermittent claudication in left calf for 3 mo. Nocturnal pain.	Atrophy of skin and nails.	Ind. short wave to spine. Intermit. venous occlusion.
(L) 110	115	160	250	150	1110	170	2400			
(R) 95	200	120	180+	140	1800	240	3000	Amputation of 2nd toe of left ft. 6 yr. before. Pain in rt. ft. for 4 mo.	Marked atrophy of skin and nails. Rose spots on both ft. Rt. big toe, red and swollen.	Referred to surgery.
(L) 85	140	95	175	135	190	140	900+			
(R) 48	35	53	40	60	240	43	360	Gangrene of toes of both ft. following radiant heat to ft. 2 wk. before.	Gangrene of toes. Atrophy of skin and nails.	Intermit. venous occlusion.
(L) 48	30	58	100	58	150	58	1800			
(R) 90	145	110	1800	140	5400+	150	3600	Infection and amputation of 4 toes on left ft. during preceding 10 yr.	Infected fissure between 3rd and 4th metatarsals on left ft. Small ulcers of skin.	Ind. short wave to spine. Conservative treatment.
(L) 125	200	150	900	125	2400+	170	2400+			
(R) 75	50	75	70	110	360	80	5400	Intermittent claudication for years. Redness and swelling of rt. ft. for 6 wk.	Gangrene of rt. ft.	Referred to surgery.
(L) 55	40	60	180	70	480	90	3600			

TABLE

PATIENTS FOLLOWED OVER A PERIOD OF TIME, ILLUSTRATING THE VALUE

SUBJECT AND DIAGNOSIS	AGE	OSCILLOMETIC READINGS			HISTAMINE TEST*	SKIN TEMPERATURE
		THIGH	LEG	FOOT		
Females	49					
H. M. (R.H.D. + A.F. + Embolus to left femoral artery.)		(R) 3	2	¼		(R) Skin temp. of big toe = 33.0° C.
		(L) ½	0	0		(L) Skin temp. of big toe = 28.7° C.
		(R) 2	3¾	0		(R) No change in big toe—27.1° C. to 26.6° C.
		(L) ⅛	0	0		(L) Increase in big toe from 29.3° C. to 30.4° C.
		(R) 2½	4¼	½	(R) Sl. delay in ft., ank. and thigh; good in leg.	(R) Skin temp. of big toe = 29.5° C.
		(L) ½	¼	0	(L) Marked delay in ank.; sl. delay in ft. and thigh; good in leg.	(L) Skin temp. of big toe = 30.2° C.
		(R) 4	5	¼		
		(L) ½	¼	S.P.		
L. D. (D.M. + Arterio-sclerosis obliterans)	52	(R) 1½	¾	0	(R) Sl. delay in ank., leg and thigh; good in ft.	(R) Skin temp. of big toe = 28.6° C.
		(L) ⅛	¼	0	(L) Mod. delay in ft. and ank., good in leg and thigh.	(L) Skin temp. of big toe = 28.1° C.

*See text for explanation of notations of the histamine test.
†Th. = Threshold in seconds.
‡C. T. = Clearing time in seconds.
D. M. = Diabetes mellitus.
A. F. = Auricular fibrillation.
R. H.D. = Rheumatic heart disease.

III

OF THE REACTIVE HYPEREMIA RING TEST IN EVALUATION OF THERAPY

REACTIVE HYPEREMIA RING TEST								PERIOD OF SYMPTOMS	LESION	THERAPY
THIGH		LEG		ANKLE		FOOT				
TH.†	C.T.‡	TH.	C.T.	TH.	C.T.	TH.	C.T.			
(R) 35	90	35	130	35	120	30	180	Tingling and burning sensations in soles of feet.	Sl. pallor of left ft. as compared to rt.	None.
(L) 53	90	40	75	20	140	40	90			
(R)		35	200	35	200	54	390	Extreme pain and coldness of left leg and ft. for 12 hr.	Pallor of left leg and ft. Dusky cyanosis of toes.	Ind. short wave to spine. Oscillating bed. Papaverine.
(L)		60	255	45	255	58	1200+			
(R) 43	65	43	93	43	100	45	105			
(L) 68	60	58	80	48	200	58	275			
								(3 mo. on oscillating bed)		
(R) 38	30	48	65	50	60	53	85	(1 mo. after cessation of oscillating bed therapy.)		
(L) 58	30	58	48	68	55	58	240	(Complete recovery)		
(R) 73	65	73	100	73	160	85	150	Ulcer of left ft. for 1 yr. Nocturnal pain.	(R) Sl. atrophy of skin and nails. (L) Healed ulcer over ext. malleolus. Ft. swollen and erythematous over dorsum.	Ind. short wave to spine.
(L) 58	45	68	140	90	225	80	340			
(R) 73	60	73	120	75	175	100	440			
(L) 65	60	70	130	85	380	160	3600+			
								(Put on oscillating bed)		
(R) 75	70	75	250	90	320	105	1200			
(L) 85	100	90	255	115	1200	110	3600+			
								(3 wk. on oscillating bed)		
(R) 68	70	68	170	65	330	80	245	(Great clinical improvement)		
(L) 75	110	85	250	98	720	180	1200	(Nails starting to grow again)		
								(6 wk. on oscillating bed)		
(R) 90	80	85	85	90	450	110	900	(Thermostatic heat cradle applied)		
(L) 80	85	85	110	98	300	270	3600+	(Exacerbation of symptoms)		
								(10 wk. on oscillating bed)		

indicated by Montgomery, et al.,[4] no great amount of information is therefore derived from such studies in clear-cut cases of organic obliterative disease of the arteries, except as collateral evidence.

One interesting observation, not generally made, was that the skin temperature in the most affected extremity was frequently higher than that of the least affected extremity; this occurred in the absence of demonstrable inflammatory lesions. It is evident that some natural mechanism exists whereby the remaining vascular channels open up once the blood supply to an extremity has reached a certain degree of obliteration and after the obliteration has persisted for a period of time. Again, oscillometric readings and reflex dilation tests do not ordinarily reveal this improvement in the local circulation. The need of a means of accurately ascertaining the functional capacity of the finer circulation is thus strikingly brought forth. Indeed, as will be demonstrated later, *the lesions and symptomatology are far more exactly related to the functional capacity of the finest vessels than to that of the larger arterial trunks.* Evidence has also been previously presented[2] that there is an expected and natural ageing of these fine vessels which is entirely independent of arteriosclerosis of the larger vessels. Furthermore, the influence of pronounced seasonal changes on the responsiveness of these fine vessels in relation to outside temperature must not be overlooked.*

The Histamine Test versus the Reactive Hyperemia Ring Test.—The histamine test, as indicated above, was done to corroborate the results of the segmental R.H.R.T.† When the histamine injection caused a wheal to appear at a particular site within two and one-half minutes, the response was regarded as normal; when the wheal appeared within five minutes it was regarded as slightly delayed, and, in ten minutes, as moderately delayed; failure to appear within ten minutes constituted a greatly delayed reaction. No attempt was made to appraise the appearance and disappearance of the local red reaction and arteriolar flare in these tests because they were found to be too variable.

As shown in Table I, there was a fair correlation between the degree of delay in the histamine responses and the extent of symptoms and lesions. However, there were many cases of marked discrepancy. In Case F. D., in the male group, the patient had only moderate delay in the ankle and slight delay in wheal formation in his left foot, but he had one of the most severe lesions of the group, namely, gangrene of the fourth and fifth toes. On the other hand, in Case M. L., also in the

*It is unfortunate that during the course of this investigation it was not possible to make accurate observations on the incidence of arteriosclerotic vascular lesions in relation to the seasons. It is the authors' casual observation, however, that the number of admissions and the morbidity of arteriosclerotic vascular lesions are greatly increased in midwinter on the various services of Kings County Hospital. Since such a seasonal variation in the number of admissions might arise from other causes, no sound conclusion may be drawn. An extended study of the effects of season on peripheral vascular disease is desirable.

†Hereafter, the reactive hyperemia ring test will be indicated by the abbreviation R. H. R. T.

male group, there were markedly delayed histamine reactions on the right foot, but only slight atrophy of the skin and nails of this foot was found on examination.

Since the clearing time of the R.H.R.T. has been shown to be related to the rate of blood flow in the skin,[1, 2] and the length of time required for the histamine wheal to appear is also said to be related to cutaneous blood flow,[3, 4, 5] a comparison of the relative worth of these two tests can be made. Considering these tests only in the foot and ankle, it may be seen from Table I that most histamine wheals which were interpreted as normal corresponded to a clearing time of less than 300 seconds. Those which were slightly or moderately delayed fell in a group of clearing times of less than 500 seconds, although some corresponded to clearing times of 1,000 or more seconds. A marked delay in the appearance of the histamine wheal in a few cases accorded with a clearing time of over 2,000 seconds. Paradoxically, in some patients a greatly delayed histamine wheal was obtained with clearing times of less than 250 seconds, and in the presence of a clinically good skin circulation, with absence of marked symptoms and lesions. The converse also was not infrequently noted (Table I).

To what causes these apparent deficiencies in the histamine wheal test may be ascribed cannot be immediately ascertained. A closer survey of the exact relationship of the segmental thresholds of reactive hyperemia in the skin of the lower extremities and the extent of vascular obliteration and symptomatology may now be undertaken, not only to explain this paradox, but also to ascertain whether, in the quantitation of these thresholds, a better means of evaluating the functional loss of the cutaneous circulation is not readily available.

The Relationship of the Type of the Lesion and the Results of the Reactive Hyperemia Ring Test.—These results must be considered against a background of the natural segmental and ageing characteristics of the skin of the lower extremities.* Since most of our subjects were in the fifth and sixth decades, the normal for these patients may be briefly stated. There is a gradual rise in the *threshold* of reactive hyperemia caused by local ischemia which rises from about 50 to 75 seconds in the upper part of the thigh to about 90 to 200 seconds in the dorsum of the foot, and the corresponding *clearing times* rise from about 60 to 90 seconds in the thigh to 100 to 300 seconds in the foot. In a few isolated cases, the clearing time normally may be as high as 600 seconds in the skin of the ankle and foot.

Invariably, in all the cases of arteriosclerosis obliterans which we studied, the segmental thresholds of reactive hyperemia in the lower extremities were in no way significantly different from the expected normal. This held true for the patients with minimal symptoms and signs, as well as for those with far-advanced lesions, such as gangrene of the toes.

*For a complete account of this subject, see preceding article in this issue.

Indeed, in some instances the threshold was considerably lower on the affected side. Case M. F., Table I, is a good example of this.

It is well known that dilation of small vessels occurs even when the circulation is completely occluded in acute experiments,[12] and it has further been shown that the threshold of reactive hyperemia caused by local ischemia in the skin is not altered under these conditions.[1, 2] What occurs when various grades of occlusion are maintained over periods of weeks or months has not been studied. Since these patients with obliterative vascular disorders really constitute a naturally conducted experiment along these lines, the results of this study actually supply the answer to this problem.

It is at once distressing and gratifying to know that there is no diminution in the capacity of these fine skin vessels to respond by reactive hyperemia to local ischemia in cases of long-standing obliteration of the vascular tree. It is disturbing, for it indicates that therapy which aims to improve the capacity of these fine vessels, such as mecholyl iontophoresis, local heat, intermittent venous occlusion, etc., are superfluous unless, of course, they also appreciably improve the blood supply to these fine vessels, especially in instances of advanced obliteration of larger arterial trunks. That these therapeutic agents are capable of achieving this in peripheral vascular disorders has not yet been thoroughly proved.[13, 14, 16, 17] On the other hand, it is pleasing to learn that, even with extreme degrees of obliterative disease, continuing over a period of years, the ability of these fine vessels to respond by hyperemia to local ischemia is in no way impaired. *This indicates that therapeutic procedures must aim largely at improving local blood flow, and need not induce hyperemia.* Perhaps this explains the success of such methods as Buerger's exercises and the oscillating bed, which passively increase local blood flow without causing dilation of vessels. Vice versa, the failure of the intermittent venous occlusion devices and the suction boot, which primarily produce intense hyperemia as a means of increasing blood flow, is explicable in the same way.*

When the clearing times of the R.H.R.T. were compared with the symptoms and extent of the lesions, an excellent correlation was found. The patients were grouped as indicated in Fig. 1. Many patients who were referred to us with a diagnosis of peripheral vascular disease had no discernible lesions of their extremities. However, on performing a modified plantar ischemia test,[7] slight pallor was noted with elevation, and some rubor with dependency, of the feet. This group of patients, along with perfectly normal ones, were placed in Group I, whereas Group II, in addition, had some atrophy of the skin and nails. To Group III were assigned those patients who, besides presenting the lesions above mentioned, also suffered from nocturnal pain and claudica-

*The authors' viewpoints concerning the efficacy of these therapeutic devices is based not only upon their own clinical experience, but also on that of others.[13, 14, 16, 17]

tion of such degree that they were not able to walk farther than two city blocks at a moderate pace before they were forced to stop and rest. Those who presented the well-known syndrome of impending gangrene were put in Group IV, and those with actual gangrene, in Group V.

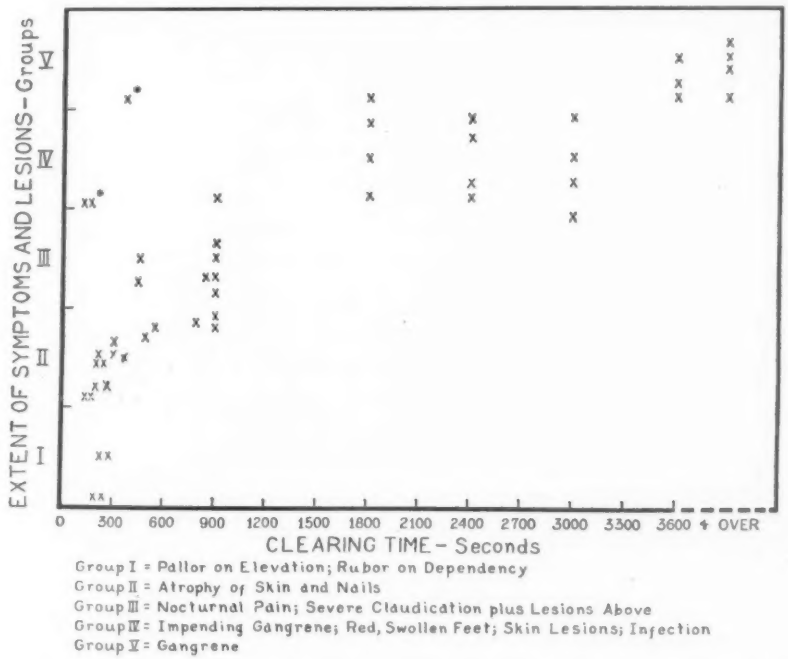
EXTENT OF SYMPTOMS AND LESIONS – Groups
V
IV
III
II
I
0 300 600 900 1200 1500 1800 2100 2400 2700 3000 3300 3600 + OVER
CLEARING TIME – Seconds
Group I = Pallor on Elevation; Rubor on Dependency
Group II = Atrophy of Skin and Nails
Group III = Nocturnal Pain; Severe Claudication plus Lesions Above
Group IV = Impending Gangrene; Red, Swollen Feet; Skin Lesions; Injection
Group V = Gangrene

Fig. 1.—The clearing times of the reactive hyperemia ring test in the ankle and foot are plotted against the severity of symptoms and extent of lesions, as grouped above. Patients marked by asterisks had received treatment which made their lesions worse (see text for discussion).

As is shown in Fig. 1, the clearing time of the R.H.R.T. was longer in proportion to increasing severity of the lesions. Thus, all patients in Group I had a clearing time of less than 300 seconds; those in Group II, one of 200 to 600 seconds; those in Group III, one of 400 to 900 seconds; and those in Group IV, one of 1,000 to 3,000; those in Group V generally had one of 3,000 seconds or over. It is interesting that two patients who fell outside the general mean (marked by asterisks in Fig. 1) had received a form of treatment which caused a lesion more advanced than the degree of their obliterative process would indicate that they should have had. These were S. S., of the females (Table I), who had an ingrown toe nail removed, and M. S., of the males (Table I), who acquired gangrene of his toes after the application of radiant heat to his feet.

Since the clearing time has been repeatedly shown by various means to be directly related to blood flow in the smallest vessels of the skin,[1, 2] the implication of these results is obvious. The skin lesions which any patient will incur in the course of his vascular disease is a result, not

TABLE II

CASES OF EMBOLISM, ILLUSTRATING THE VALUE OF THE REACTIVE HYPEREMIA RING TEST IN INDICATING THE FORM OF THERAPY AND THE PROGNOSIS

SUBJECT AND DIAGNOSIS	AGE	OSCILLOMETIC READINGS			HISTAMINE TEST*	SKIN TEMPERATURE	REACTIVE HYPEREMIA RING TEST								PERIOD OF SYMPTOMS	LESION	THERAPY
							THIGH		LEG		ANKLE		FOOT				
		THIGH	LEG	FOOT			TH.†	C.T.‡	TH.	C.T.	TH.	C.T.	TH.	C.T.			
Females	68																
L. L. (D.M. + A.S.H.D. + A.F. + Embolus to left femoral artery)		(R) 1¾	2¼	¼	(R) Good in all parts.	(Not done)	(R) 53	40	55	60	55	118	85	255	Intense pain and coldness of left leg and ft. for 24 hr.	Pulseless, cold left ft. Dusky cyanotic toes.	Pavaex boot. Papaverine.
		(L) 2¼	0	0	(L) Marked delay at all points below knee.		(L) 60	35	65	190	75	400	120	3600+			
A. H. (R.H.D. + A.F. + Embolus to left femoral artery)	42	(R) 5	5	¼	(R) Good in all parts.	(R) Skin temp. of big toe = 29.0° C.	(R) 75	60	75	220	70	720	90	480	Intense pain, coldness and pallor of entire left leg for 8 hr.	Pulseless, cold left leg.	Referred to surgery.
		(L) 0	0	0	(L) Marked delay at all points below midthigh. Complete absence of wheal below knee.	(L) Skin temp. of big toe = 24.0° C.	(L) 150	120	240	1800	(Complete absence of hyperemia after stimulation for 10 min.)						

*For explanation of notations of the histamine test see text.
†Th. = Threshold in seconds.
‡C. T. = Clearing time in seconds.
D. M. = Diabetes mellitus.
A. F. = Auricular fibrillation.
R. H. D. = Rheumatic heart disease.
A. S. H. D. = Arteriosclerotic heart disease.

of a diminution in the ability of these fine vessels to respond to injury by reactive hyperemia, but simply of the degree of slowing of blood flow within them.

The Reactive Hyperemia Ring Test in Cases of Embolism.—Segmental quantitation of the threshold and clearing times of reactive hyperemia in the skin of an extremity with an embolus in its major artery was found to be not only an excellent aid in indicating the form of therapy to be used, but also a prognostic method. Two illustrative cases are listed in Table II. Both patients were referred to us with a diagnosis of embolism of the femoral artery. In case L. L. (Table II) the patient was found, clinically and oscillometrically, to have all the signs of this condition. However, the R.H.R.T. showed readings which were not far from normal down to the ankle, and, in the foot, no worse than had been observed in many cases of long-standing arteriosclerosis obliterans. Consequently, conservative therapy was instituted, with satisfactory results.

On the other hand, in case A. H. the patient presented a much more serious clinical picture and the question of performing embolectomy arose. Because the R.H.R.T. showed a remarkable rise of threshold and clearing time, even in the thigh, and complete absence of any response in the leg and foot, even after application of local ischemia for a period as long as 10 minutes, it was felt that a surgical procedure was indicated, and that the limb could not be saved by conservative measures. Unfortunately, the patient died of cerebral embolism before she could be operated upon.

In the interest of brevity, no other similar cases will be described, but it is clear that when it is impossible to obtain a hyperemia response after application of the weighted ring to the skin for a reasonable period of time (10 minutes), not only is there complete cessation of blood flow in these fine vessels, but, also, irreparable damage has probably taken place. This statement is made because, in acute experiments, in which complete stagnation of blood flow is produced by a tourniquet, the hyperemia response is easily obtained,[1, 2] and it is only the clearing time which is markedly altered. In addition, even with systemic anoxemia of only 30 minutes' duration, there is a very marked decrease in the sensitivity of these fine vessels,[15] indicating that prolonged oxygen lack may cause extensive damage.

When, however, with embolism of a major artery, the segmental thresholds and clearing times do not differ significantly from those in cases of the most severe arteriosclerosis obliterans (see Table I), it is reasonable to assume that the limb can be saved by conservative measures. One such case is H. M., in Table III.

Evaluation of Therapy by Means of the Reactive Hyperemia Ring Test.—We were fortunate in that we did this test on patient H. M., Table III, before complete embolism of the left femoral artery had taken place. She was referred to us because she complained of tingling

and burning sensations in the soles of her feet. Despite the presence of auricular fibrillation, and because her skin circulation was so nearly normal, it was felt that the diagnosis of embolism was questionable, and that she might instead be suffering from an obliterative vascular disorder. Twelve hours later, however, she experienced sudden, sharp, severe pain in her left foot. At this time the R.H.R.T. showed a remarkable change. Clearing times were more than doubled in the affected leg, and, in the foot, rose to over twenty minutes. Noteworthy, too, is the fact that the oscillometer readings did not change significantly. She was treated with an oscillating bed and indirect short wave diathermy to the lower part of the spine. Three months later the clearing times had returned to almost normal levels, and one month later, after cessation of hospital treatment, she showed even further improvement, with complete symptomatic recovery (Table III).

Another patient (L. D., Table III) is illustrative of the conservatism needed in the treatment of advanced obliterative vascular disease. Early in the fall her R.H.R.T. showed slight impairment of the skin circulation. She was given conservative treatment, but, because of her lack of cooperation, her lesion became worse, and she was forced to enter the hospital in December.* The clearing time of the R.H.R.T. in the foot rose to more than one hour at this time. She was put on an oscillating bed. At the end of three weeks the R.H.R.T. showed an even greater slowing of skin circulation, but at the end of six weeks there had been considerable improvement, as measured by this test (Table III). The clinical picture also was changed for the better. The nails had started to grow afresh, and the nocturnal pain was much diminished. At this time it was thought that a thermostatic heat cradle, applied to the feet, would speed recovery. The thermostatic mechanism failed to work, however, which permitted the environmental temperature about the feet to rise to excessive levels. There was again an exacerbation of symptoms, and the R.H.R.T. showed slowing of skin circulation almost to pretherapy levels.

In the above cases, therefore, the R.H.R.T. was the only criterion upon which reliance could be placed in following the course of therapy. It is well known that oscillometric readings are rarely improved by therapy. Thermometry is more useful for vasodilation tests and in vasospastic disorders than in arteriosclerosis obliterans. The histamine test is not quantitative enough to be an accurate guide of the efficacy of therapy. Plethysmographic studies are beyond the scope of ordinary clinical facilities. A simple, reliable bedside test which is capable of indicating the local blood flow in the skin is the clearing time of the R.H.R.T. This should prove to be valuable because it is the circulation in these finest vessels upon which ultimately rests the maintenance of the

*This case illustrates the authors' observation that seasonal changes may alter the course of a peripheral vascular lesion. It may well be that the advent of cold weather exerted an adverse influence upon this patient's lesions.

functions of the skin, and for which therapeutic procedures are instituted, and it is these which determine resistance against infections and pregangrenous changes.

SUMMARY AND CONCLUSIONS

Twenty-four cases of typical arteriosclerosis obliterans were carefully studied by the usual oscillometric and thermometric methods and histamine wheal tests, and also by ascertaining the segmental thresholds of reactive hyperemia in the lower extremities, using a method recently developed. The relationships of these tests to each other and to the natural gradient and ageing variations of reactive hyperemia in the human skin are described. The inadequacies of the several existing tests are pointed out. A simple reactive hyperemia ring test has been shown to be a reliable means of evaluating the skin circulation of the lower extremities in arteriosclerosis obliterans.

Two cases of embolism of the femoral artery and two patients who received a particular form of therapy and were followed over a long period of time are described to further demonstrate the implications and value of the reactive hyperemia ring test in these conditions.

The following conclusions were reached:

1. There is no exact correlation between slowing of the skin circulation and oscillometric readings.

2. There is, in general, fair agreement between the delay in histamine wheal formation and the clearing time of the reactive hyperemia ring test.

3. The thresholds of the reactive hyperemia ring tests in the ankle and foot are the same as the expected normal for the age group involved. This means that there is no decrease in the capacity of the smallest blood vessels of the skin to respond by reactive hyperemia to local ischemia, even in advanced stages of obliteration of arterial trunks.

4. The clearing times of the reactive hyperemia ring tests are directly proportional to the severity of symptoms and extent of lesions in the ankle and foot. Although the normal clearing time in the foot is under 300 seconds, it may rise to over 3,600 seconds in a foot with gangrenous changes.

5. The loss of function of the fine skin vessels, which renders the skin susceptible to infection and grangrene in the ankle and foot, is not caused by inability of these vessels to respond by reactive hyperemia, but merely by a profound slowing of blood flow within them.

6. In cases of complete embolic obstruction of the major arteries of the lower extremities, the small skin vessels may completely lose the ability to respond to local ischemia by reactive hyperemia. On the other hand, with partial embolic obstruction, or with good collateral blood flow, the hyperemia responses are comparable to those in cases of advanced arteriosclerosis obliterans.

7. The reactive hyperemia ring test offers a simple, exact, objective method of evaluating the effect of therapy, over a long period of time, upon the skin circulation of the lower extremities.

We wish to express our sincere gratitude to Dr. S. R. M. Reynolds, now at the Carnegie Institution of Washington. His unfailing inspiration and material aid have made this work possible.

REFERENCES

1. DiPalma, J. R., Reynolds, S. R. M., and Foster, F. I.: Reactive Hyperemia in Human Skin: Individual and Seasonal Variations, AM. HEART J. **23**: 377, 1942.
2. DiPalma, J. R., and Foster, F. I.: The Segmental and Ageing Variations of Reactive Hyperemia in Human Skin, AM. HEART J. **24**: 332, 1942.
3. Kramer, D. W.: Manual of Peripheral Vascular Disorders, Philadelphia, 1940, The Blakiston Co.
4. Montgomery, H., Naide, M., and Freeman, N. E.: The Significance of Diagnostic Tests in the Study of Peripheral Vascular Disease, AM. HEART J. **21**: 780, 1941.
5. Starr, I.: The Value of the Cutaneous Histamine Reaction in the Prognosis of Pedal Lesions in Diabetes Mellitus, Am. J. Med. Sc. **188**: 548, 1934.
6. McClure, W. B., and Aldrich, C. A.: Time Required for the Disappearance of Intradermally Injected Salt Solution, J. A. M. A. **81**: 293, 1923.
7. Buerger, L.: Circulatory Disturbances of the Extremities. Philadelphia, 1924, W. B. Saunders Co.
8. de Takáts, G.: The Cutaneous Histamine Reaction as a Test for Collateral Circulation in the Extremities, Arch. Int. Med. **48**: 769, 1931.
9. Gibbon, J. H., and Landis, E. M.: Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, J. Clin. Investigation **11**: 5, 1932.
10. Bennett, R. L., Hines, E. A., and Krusen, F. H.: Effect of Short Wave Diathermy on the Cutaneous Temperatures of the Feet, AM. HEART J. **21**: 490, 1941.
11. Homans, J.: Circulatory Diseases of the Extremities, New York, 1939, The Macmillan Co.
12. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, 1927, Shaw & Sons, Ltd.
13. Abramson, D. I.: The Vasodilating Action of Various Therapeutic Procedures Which are Used in the Treatment of Peripheral Vascular Disease, AM. HEART J. **21**: 756, 1941.
14. Wright, I. S.: The Conservative Treatment of Occlusive Arterial Disease, New England J. Med. **225**: 805, 1941.
15. DiPalma, J. R., Reynolds, S. R. M., and Foster, F. I.: Measurement of the Sensitivity of the Smallest Blood Vessels of the Human Skin: Responses to Graded Mechanical Stimulation in Normal Men, J. Clin. Investigation **20**: 333, 1941.
16. Veal, J. R. and McCord, W. M.: Blood Oxygen Changes Following Intermittent Venous Occlusion, AM. HEART J. **17**: 401, 1939.
17. Allen, E. V., and McKechnie, R. E.: Effect of Intermittent Venous Occlusion on the Circulation of the Extremities: Studies of Skin Temperatures, J. Lab. & Clin. Med. **22**: 1260, 1937.

CARDIOVASCULAR EFFECTS OF DESOXYCORTICOSTERONE ACETATE IN MAN

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THE fundamental importance of adrenal cortical hormones in muscular metabolism and activity is obvious from the typical muscular adynamia in Addison's disease and after experimental adrenalectomy, and from its abolition through treatment with cortical extracts. Similar phenomena apply to the vascular tone of the blood vessels as manifested in the blood pressure level.

Indications of myocardial weakness after adrenalectomy and in Addison's diseases were recorded by several investigators,[1-4] and the heart was found to be markedly reduced in size in these conditions.[3, 5-7]

On the other hand, there is also evidence that an excess of cortical hormonal substances is likely to interfere with normal heart action and size, as demonstrated by:

(a) the occurrence of congestive heart failure in patients with adrenal cortical tumors;[8]

(b) the appearance of marked cardiac dilatation with dyspnea, pulmonary and peripheral edema in Addison patients treated with an overdosage of cortical extracts or desoxycorticosterone acetate;[9-16]

(c) the appearance in the heart muscle of the rat of abnormally large amounts of adrenalin-like substances after injections of desoxycorticosterone acetate;[7]

(d) the presence of an abnormal amount of adrenalin in the enlarged and dilated heart muscle of a patient with tumors of the cortex who had died from congestive heart failure.[17]

(e) the production of changes of the electrocardiogram (T waves) of dogs through the administration of desoxycorticosterone acetate.[18]

Furthermore the suprarenal cortical hormones appear to participate in the maintenance of pathologically high blood pressure levels. Experimental renal hypertension is partly dependent upon the presence of cortical hormonal material;[19, 20, 21] abnormal elevation of the blood pressure following the administration of cortical sterols has been observed in animals[22, 23] and in patients with[12, 16, 24] or without Addison's disease.[25] Hyperplasia and adenomas of the suprarenal cortex are common features in persons with essential hypertension.[8, 26, 27]

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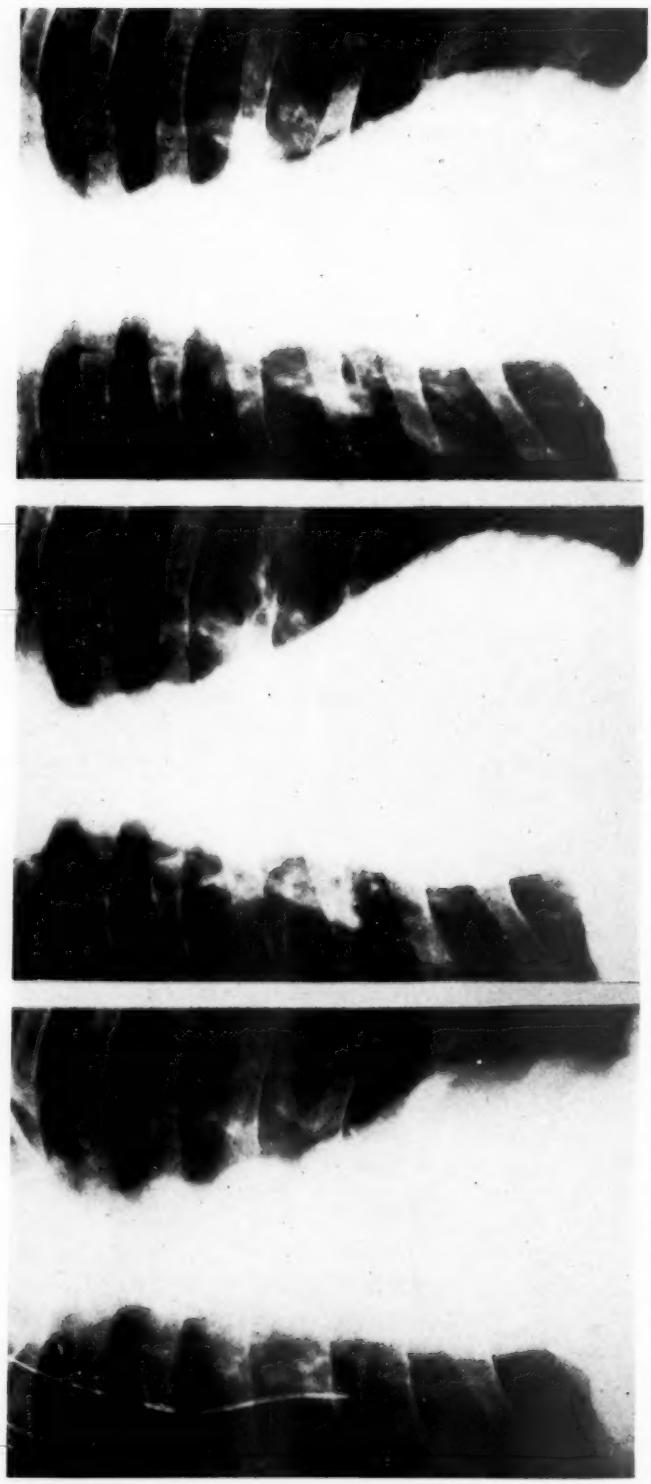

Fig. 1.—Case 3. The heart before treatment, immediately following five daily injections of desoxycorticosterone acetate (20 mg. each) and one week later.

The above-mentioned facts are suggestive of a pathogenic role of cortical sterols in the pathogenesis of arterial hypertension and of myocardial damage and failure. It appeared interesting, therefore, to study the effect of such substances upon the normal human heart and vascular system.

Desoxycorticosterone acetate was used for this purpose since it is the most readily available of the various physiologically active cortical sterols although it is known that other cortical fractions exert a more marked influence, at least upon the skeletal muscle.[28]

Apart from a few experiments in which "Cortate"* was used, most experiments were carried out with "Doca."†

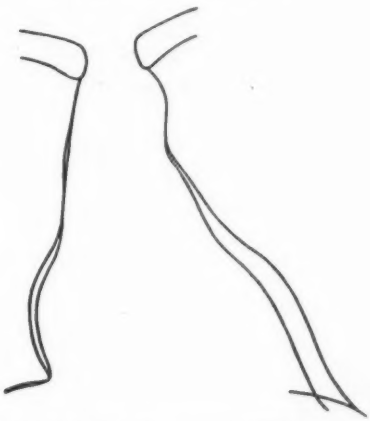

Fig. 2.—Case 8. The heart before treatment (inner contour) and immediately following three daily injections of desoxycorticosterone acetate (50 mg. each) (outer contour).

PROCEDURE

Eleven healthy male students and one patient with bronchial asthma were treated for varying numbers of days (three to fourteen) with daily intramuscular doses of 20 to 50 mg., totaling 100 to 330 mg. of desoxycorticosterone acetate (d. c. a.).

The following features were recorded before and during the treatment and twenty-four hours after the last injection: blood pressure, pulse rate, roentgenogram of the heart, electrocardiogram, body weight, concentration of adrenalin and adrenalin-like compounds in the blood and their "specific ratio,"[21] effect of adrenalin injection and of physical[29] exercise upon blood pressure, pulse rate and electrocardiogram.

BLOOD PRESSURE

There were no characteristic changes except a moderate rise of the systolic pressure in two cases (Cases 4 and 10) at the time of the conclusion of the experiments.

*Schering.

†A very generous supply had been received from the Roche Organon, Inc.

PULSE RATE

In eight cases there were no characteristic changes. In three of the healthy students there was a temporary tachycardia: in Case 4 108 vs. 84 beats; in Case 10 110 vs. 75 beats, only on the second and third days; in Case 9 112 vs. 84 beats, only on the second day.

In Case 12 (a patient with bronchial asthma) a marked bradycardia prevailed for the duration of the experiment. The pulse rate decreased steadily from 80 to 48 beats per minute.

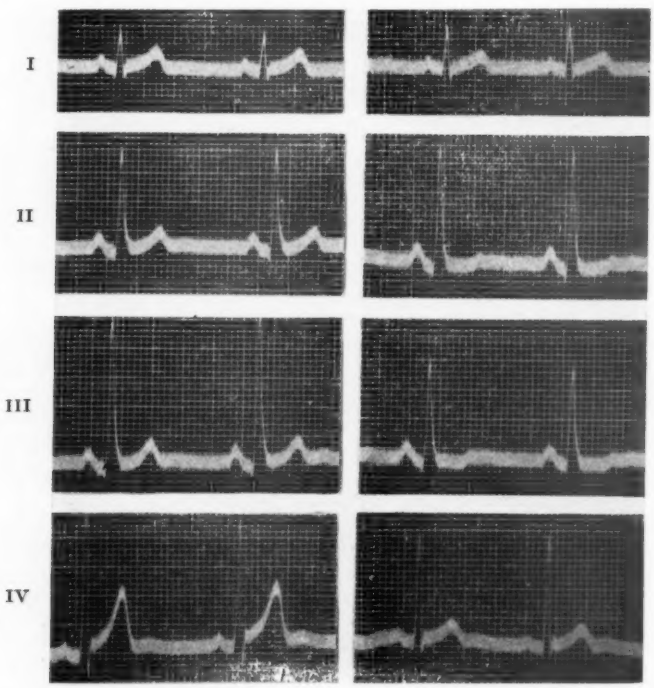

Fig. 3.—Case 8. Electrocardiogram before and four weeks after desoxycorticosterone acetate injection.

DIAMETER OF THE HEART

In making radiograms of the heart before and after the treatment with d. c. a. care was taken to duplicate the position of the diaphragm as accurately as possible in order to obtain comparable results.

In nine of the twelve cases there were enlargements of the diameter of the heart shadow ranging from +4 to +17 mm. with an average of +6 mm. These enlargements concerned only the ventricles and disappeared again within about a week after discontinuation of the drug (Figs. 1 and 2).

ELECTROCARDIOGRAM

The electrocardiograms taken after the d. c. a. treatment as compared with the controls taken before the d. c. a. injections showed distinct

alterations of the "anoxic" type in those two students (Cases 8 and 9) who had received the highest single doses (50 mg. per day), namely, lowering or inversion of the T waves and depression of the S-T segments which persisted from a few days to as much as 4 weeks (Figs. 3 and 4).

A survey of the electrocardiograms of all of the eleven healthy students showed that lowering of the T waves was the only feature commonly observed (Table II). It was present in the first lead in six cases, in the second lead in eight cases, in the third lead in nine cases, in the fourth lead in seven cases.

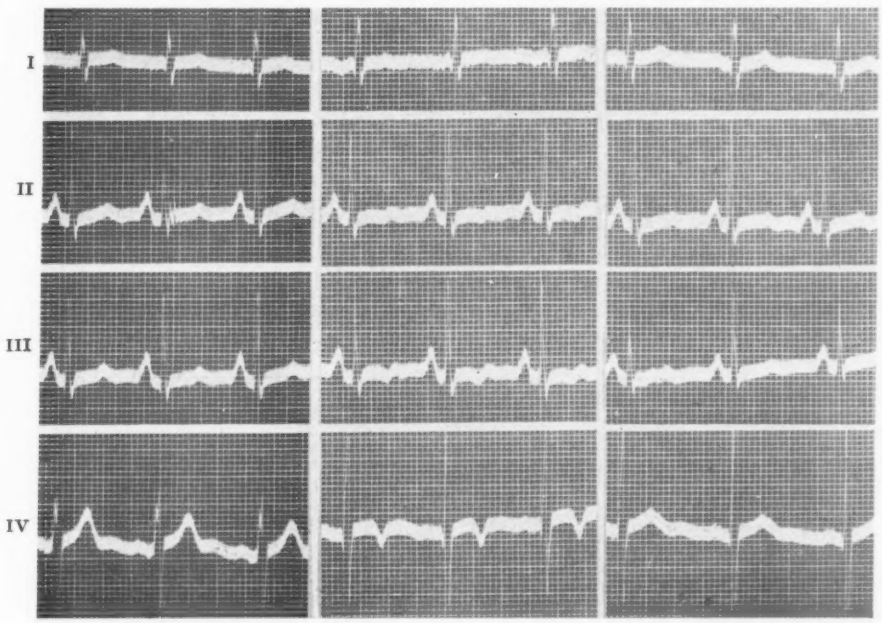

Fig. 4.—Case 9. Electrocardiogram at rest before desoxycorticosterone acetate, twenty-four hours after last desoxycorticosterone acetate injection, and again one week later.

In Case 7 the P wave was almost completely absent in Leads II and III (Fig. 5) after the d. c. a. injections.

The R wave was somewhat lowered in the third lead in five cases.

In Case 12, a 37-year-old patient with bronchial asthma, emphysema, a small heart and some cyanosis, the electrocardiogram was abnormal from the beginning. The injections were followed by marked bradycardia and changes of the P and T waves in the three first leads and of the QRS complex in the first lead (Fig. 6).

BODY WEIGHT

There was an increase in weight in all instances beginning with the day of the first injection and ranging from 1.25 to 6.5 lb. The maxima were reached between the second and eighth days of treatment.

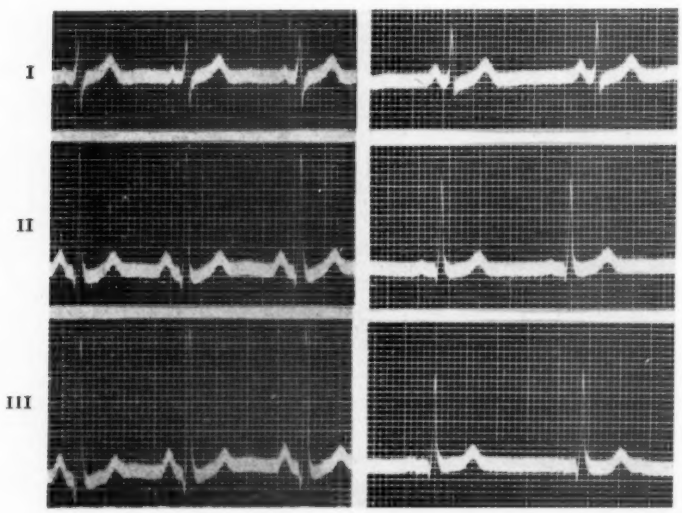

Fig. 5.—Case 7. Electrocardiogram at rest before and twenty-four hours after desoxycorticosterone acetate injections.

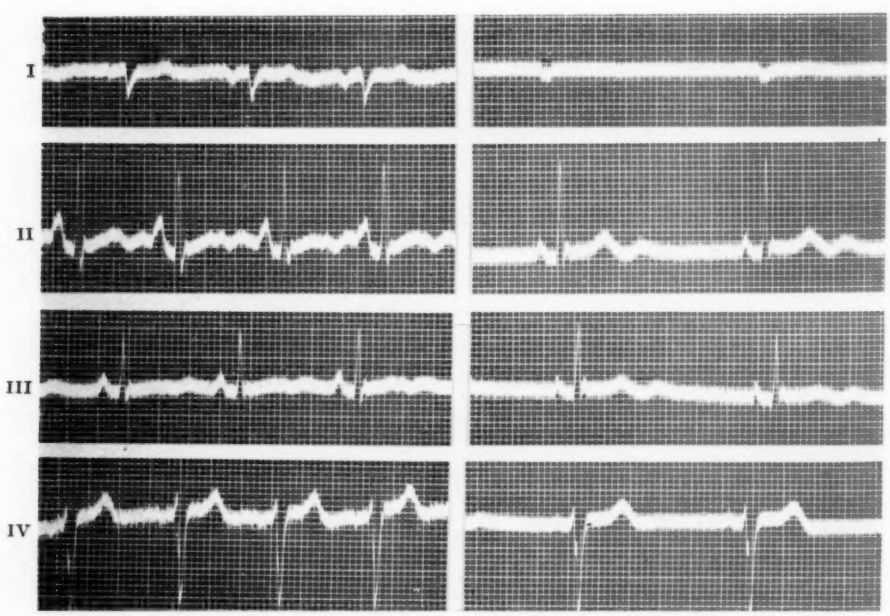

Fig. 6.—Case 12 (bronchial asthma). Electrocardiogram at rest before and twenty-four hours after desoxycorticosterone acetate injections.

LEVEL OF ADRENAL HORMONES IN THE BLOOD

The determinations were done before the first and twenty-four hours after the last injection. The colorimetric findings obtained with the modified method of Shaw[29] were originally believed to be composed of both adrenalin and of cortical sterols bound to it.[7, 29, 30] However, recent investigations which were carried out upon the suggestion of Dr. E. C. Kendall make the direct participation of sterols doubtful and make it appear more likely that the results are due chiefly to adrenalin plus certain adrenalin-like compounds (sympathin? adrenalone?).

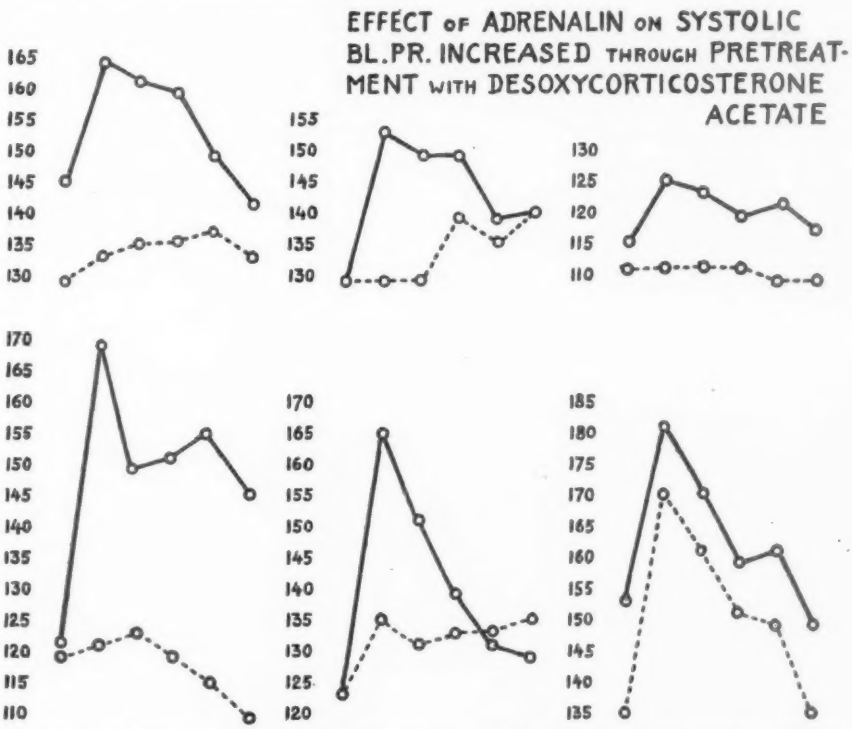

Fig. 7.—The blood pressure readings were taken at intervals of six minutes, before and following the subcutaneous injection of 0.4 to 0.5 mg. of adrenalin. Dotted lines, before treatment with d.c.a.; solid lines, after treatment with d.c.a.

While the behavior of the total colorimetric values was found to be uncharacteristic after injections of d. c. a., there was in all but two instances a fall of the "specific ratio," indicating a higher proportion of adrenalin proper taking part in the total colorimetric findings.

ALTERED EFFECT OF ADRENALIN INJECTION

The effect of subcutaneously injected adrenalin (0.4 to 0.5 mg.) upon the systolic blood pressure was markedly increased in all six persons pretreated with d. c. a. (Fig. 7), while the reactions of the diastolic pressure and of the pulse rate remained practically unchanged.

TABLE I

CASE NO.	AGE (YEARS)	TOTAL DOSE (MG.)	GIVEN IN DAYS	BLOOD PRESSURE		PULSE RATE		CHANGE IN HEART DIAMETER (MM.)	INCREASE IN BODY WEIGHT (LB.)	ADRENAL HORMONES IN BLOOD (COLOR UNITS)		SPECIFIC RATIO OF ADRENAL HORMONES	
				BEFORE D.C.A.	AFTER D.C.A.	BEFORE D.C.A.	AFTER D.C.A.			BEFORE D.C.A.	AFTER D.C.A.	BEFORE D.C.A.	AFTER D.C.A.
1	23	100	5	124/60	124/66	78	80	+ 9	2.5	169	100	1:1.20	1:1.43
2	25	100	5	120/60	116/60	70	64	0	4	152	194	1:1.06	1:1.41
3	25	100	5	114/70	116/70	72	62	+17	3	139	193	1:1.00	1:1.43
4	24	110	4	136/84	154/84	84	108	- 3	1.5	70	139	1:1.29	1:1.74
5	26	120	4	130/88	130/80	76	82	+ 5	5	50	77	1:0.81	1:1.54
6	22	150	5	112/70	116/72	94	84	- 3	3	169	169	1:1.13	1:1.49
7	25	150	5	112/66	120/78	84	78	+ 5	1.25	159	62	1:1.27	1:1.82
8	26	150	3	116/74	116/70	72	72	+14	1	112	110	1:1.60	1:1.32
9	31	150	3	148/96	146/102	84	96	+ 9	1.5	60	57	1:1.20	1:1.32
10	23	160	4	122/72	142/60	75	72	+11	5.5	103	156	1:0.76	1:1.11
11	24	330	14	122/72	117/67	74	80	+ 7	6.5	146	102	1:1.32	1:1.27
12*	37	120	6	130/80	146/90	80	48	+ 4	3	286*	240	1:1.27	1:1.41
Av.	26	150	5	124/74	129/74	78	76	+ 6	3.2	135	133	1:1.16	1:1.44

*Bronchial asthma, abnormally high blood level of adrenal hormones, abnormal electrocardiogram.

In all instances there was a slight lowering of the T waves in at least two leads of the adrenalin electrocardiograms (taken twelve minutes after the injection) after pretreatment with d. c. a. compared with those which had been taken after adrenalin injection without d. c. a. pretreatment (Table II).

TABLE II

AVERAGE CHANGE IN THE HEIGHT OF THE T WAVES AFTER TREATMENT WITH DESOXYCORTICOSTERONE ACETATE

	D.C.A.* ALONE (MM.)	ADRENALIN† S.C. (MM.)	PHYSICAL EXERCISE‡ (MM.)
Lead I	-0.1	-0.15	-0.3
Lead II	-0.9	-0.4	-0.9
Lead III	-1.3	-0.9	-0.9
Lead IV	-3.0	-1.7	-4.0

*Electrocardiogram at rest after treatment with d.c.a. compared with electrocardiogram at rest before d.c.a.

†Electrocardiogram twelve minutes after adrenalin injection after pretreatment with d.c.a. compared with electrocardiogram twelve minutes after adrenalin injection before d.c.a.

‡Electrocardiogram two minutes after exercise after pretreatment with d.c.a. compared with electrocardiogram two minutes after exercise before d.c.a.

ALTERED EFFECT OF PHYSICAL EXERCISE

In six cases twenty genuflexions were performed before the first and twenty-four hours after the last d. c. a. injection. The reactions of the blood pressure immediately following exercise did not show any significant change (average increase 18 vs. 21 mm. systolic), and neither did the pulse rate (average increase 34 vs. 29 beats per minute).

Electrocardiograms were taken two minutes after exercise. In all instances there was an increased lowering or inversion of the T waves in at least two leads in the exercise electrocardiograms after pretreatment with d. c. a. as compared with those taken before the d. c. a. injections (Table II).

SUBJECTIVE SENSATIONS

In only two cases did there occur subjective sensations attributable to the treatment with d. c. a. In one case (Case 4) these consisted of precordial oppression on exertion (walking) which began on the third day of the d. c. a. treatment and disappeared again three days after the latter had been discontinued. In another case (Case 3) with marked enlargement of the heart there was some palpitation although the pulse rate was not significantly altered.

A marked intensification of the palpitation and dyspnea following the injection of adrenalin was observed in four of six cases pretreated with d. c. a. In two of six pretreated cases physical exercise (genuflexions) caused increased shortness of breath.

DISCUSSION

The most characteristic cardiovascular features observed after the administration of desoxycorticosterone acetate (d. c. a.) were an in-

crease of the diameter of the heart, changes of the electrocardiogram of the anoxic type, both at rest and after injection of adrenalin or after physical exercise, and a marked intensification of the effect of injected adrenalin upon the blood pressure.

A close interrelation of the suprarenal cortex and medulla is suggested by their morphological and vascular arrangement,[31, 32, 33] by a parallelism of their vascular reactions to certain stimuli,[34] by chemical relations between cortical lipids and adrenalin,[35, 36, 37, 38] by the fact that the administration of d. c. a. in the rat is followed by an accumulation of adrenalin-like substances in the heart, kidney and liver[7] and by the intensification of the vascular effects of adrenalin through "Cortin."[39]

The above-described observations on human beings are confirmatory of such a relationship. It appears possible that the effects of d. c. a. upon the heart and blood vessels are at least in part brought about by an increase of the secretion, deposition in the tissues and functional efficacy of adrenalin and related substances.

The blood pressure resting level was not significantly altered by the administration of d. c. a. while in patients with Addison's disease[12-16, 24] and other conditions,[25] and in animals[22, 23] hypertensive reactions have been observed after injections of d. c. a.

The enlargement of the heart which is the logical contrast to the diminution of the heart size in adrenal cortical deficiency[3, 5-7] parallels that observed in Addison patients during treatment with d. c. a.[24]

The regular early increase in body weight, which was obviously due to the retention of water, must not be interpreted as an indication of cardiac failure but rather as "edema of adrenal origin."[24]

The appearance of "anoxic" changes of the electrocardiogram, chiefly affecting the T wave, both at rest and intensified after physical exercise and after injection of adrenalin, further stresses the similarity of the effect of d. c. a. with that of adrenalin.[40] It is in agreement with alterations of the T wave observed in dogs during treatment with d. c. a.[18]

While the subjective sensations of palpitation and dyspnea were increased in several of the persons pretreated with d. c. a. after physical exercise and after injection of adrenalin, there was one person who complained of angina-like symptoms during and after the treatment with d. c. a. alone. In this case there was also a moderate degree of tachycardia, a moderate elevation of the blood pressure level, and the greatest adrenalin sensitivity in regard to the reaction of the blood pressure after treatment with d. c. a.

The provocation of anginal symptoms through d. c. a. is reminiscent of analogous observations in persons treated with testosterone[41] and it is well compatible with the theory that angina pectoris on effort is caused by the local anoxia-producing effect of adrenalin upon the myocardium.[42, 43] It seems possible at least that this process of adrenalin anoxia of the heart muscle is also intensified by d. c. a., quite apart from the

fact that abnormally intense discharges of adrenalin into the blood stream immediately following physical exercise were found to be a characteristic of angina patients.[44]

Most important appears the question whether or not d. c. a. as such or in combination with adrenalin plays any causal role in the pathogenesis of so-called "hypertensive" or "idiopathic" heart disease, particularly in those forms in which little or no coronary sclerosis is involved.[45] As pointed out in the introduction of this paper (items a-e) there exists a variety of clinical and experimental facts strongly suggestive of such a conception. It is further stressed by the results of the above-discussed experiments with desoxycorticosterone acetate in normal persons and by the presence of abnormally large amounts of adrenalin and adrenalin-like substances in the blood[30] and in the heart muscle[17] of patients with congestive heart failure.

The mutual relationship between dilatation and hypertrophy of the heart on one side and abnormally high blood pressure on the other is not an obligatory one, as demonstrated by the experimental results discussed in this paper and by the not infrequently observed but seldom mentioned clinical cases of large hearts without hypertension and without coronary sclerosis. However, the same damaging agent which causes cardiac muscular hypertrophy and dilatation may cause in a similar way arteriolar muscular hypertrophy or arteriolar sclerosis and thus contribute to the elevation of blood pressure. Adrenalin-like compounds have been found in the tissue of arterial walls.[17]

The usual conception of "cardiac" edema as a merely physical phenomenon of hemodynamic and hydrostatic nature will probably require a thorough revision with consideration of the hormonal factors involved.

It should be re-emphasized that desoxycorticosterone acetate is only one of the "surprisingly large number of steroid derivatives of the adrenal cortex, many of which are physiologically active."[28] Its isolated effects as produced experimentally cannot possibly tell the whole story of the apparent hormonal pathogenesis of myocardial metabolic and structural pathology, but they are an impressive indicator of the fact that cardiology and endocrinology are beginning to overlap to an extent which would hardly have been thought of only a few years ago.

CONCLUSIONS

In healthy young men and in a patient with bronchial asthma the following effects of desoxycorticosterone acetate (Doca and Cortate) administered over periods of several days were observed:

1. Enlargement of the heart.
2. Anoxic changes of the electrocardiogram (persisting from few days to four weeks).
3. Moderate tachycardia or bradycardia.

4. Anginal complaints in one case.

5. Intensification of the effect of adrenalin upon the systolic blood pressure and of the accompanying subjective sensations.

6. Slightly increased anoxic changes of the electrocardiogram after injection of adrenalin and after physical exercise, as compared with the responses to the same stimuli before pretreatment with d. c. a.

7. Increase of body weight.

8. Increase of the relative concentration of blood adrenalin as compared with the amounts of other adrenalin-like substances.

The significance of the effects of cortical sterols and adrenalin upon the cardiovascular system is discussed in regard to the probable hormonal pathogenesis of the so-called "hypertensive" or "idiopathic" types of heart disease.

REFERENCES

1. Cleghorn, R. A., Armstrong, C. W. J., Austen, D. C., and McVicar, G. A.: The Response of the Denervated Nictitating Membrane and of Blood Pressure to Sympathetic Nerve Stimulation in Adrenalectomized Cats, Am. J. Physiol. **132**: 542, 1941.
2. Hall, G. E.: Experimental Heart Disease, Arch. Int. Med. **12**: 907, 1939.
3. Rowntree, L. G., and Snell, A. M.: A Clinical Study of Addison's Disease, Philadelphia and London, 1931, W. B. Saunders Co.
4. Albers, D., and Thaddea, S.: Elektrokardiographische Veraenderungen bei experimenteller und klinischer Nebenniereninsuffizienz, Ztschr. f. Kreislaufforsch. **29**: 825, 1937.
5. Barker, N. W.: The Pathologic Anatomy in 28 Cases of Addison's Disease, Arch. Path. & Lab. Med. **8**: 432, 1929.
6. McGavack, T. H.: Changes in Heart Volume in Addison's Disease and Their Significance, AM. HEART J. **21**: 1, 1941.
7. (a) Raab, W.: Chemical Determinations of the Adreno-Cortical (AC) Hormones in the Heart Muscle of the Rat, Endocrinology **29**: 564, 1941.
   (b) Raab, W.: Distribution of Adreno-Cortical (AC) Hormones in Tissues of the Rat Under Normal and Experimental Conditions, Endocrinology **29**: 126, 1941.
8. Hantschmann, L.: Nebennierenrindentumoren und Hochdruck, Klin. Wchnschr. **20**: 394, 1941.
9. Heni, F.: Klinisches zur Frage des Morbus Addison, Klin. Wchnschr. **18**: 1052, 1939.
10. Pantschew, A.: Folgen der Ueberdosierung des Nebennierenrindenhormons, Klin. Wchnschr. **18**: 1570, 1939.
11. Thorn, G. W., and Emerson, K.: The Role of Gonadal and Adrenal Cortical Hormones in the Production of Edema, Ann. Int. Med. **14**: 757, 1940.
12. McCullagh, E. P., and Ryan, E. J.: Use of Desoxycorticosterone Acetate in Addison's Disease, J. A. M. A. **114**: 687, 1940.
13. Kepler, E. J.: Treatment of Addison's Disease With Desoxycorticosterone Acetate, J. A. M. A. **114**: 688, 1940.
14. Rynearson, E.: Treatment of Addison's Disease With Desoxycorticosterone Acetate, J. A. M. A. **114**: 688, 1941.
15. Wilson, D. M., Rynearson, E. H., and Dry, T. J.: Cardiac Failure Following Treatment With Desoxycorticosterone Acetate, Proc. Staff Meet., Mayo Clin. **16**: 168, 1941.
16. Soffer, L. J., Engle, F. L., and Oppenheimer, B. S.: The Treatment of Addison's Disease With Desoxycorticosterone Acetate, J. A. M. A. **115**: 1860, 1940.
17. Raab, W.: In Preparation.
18. Kuhlmann, D., Ragan, Ch., Ferrebee, J. W., Atchley, D. W., and Loeb, R. F.: Toxic Effects of Desoxycorticosterone Esters in Dogs, Science **90**: 496, 1939.

19. Page, I. H.: The Effect of Bilateral Adrenalectomy on Arterial Blood Pressure of Dogs With Experimental Hypertension, Am. J. Physiol. **122**: 352, 1938.
20. Collins, D. A., and Wood, E. H.: Experimental Renal Hypertension and Adrenalectomy, Am. J. Physiol. **123**: 224, 1938.
21. Friedman, B., Somkin, E., and Oppenheimer, E. T.: The Relation of Renin to the Adrenal Gland, Am. J. Physiol. **128**: 481, 1940.
22. Grollman, A., Harrison, T. R., and Williams, J. R.: The Effect of Various Sterol Derivatives on the Blood Pressure of the Rat, J. Pharmacol. & Exper. Therap. **69**: 149-155, 1940.
23. Rodbard, S., and Freed, S. C.: The Effect of Desoxycorticosterone Acetate on the Blood Pressure of the Dog, Endocrinology **30**: 365, 1942.
24. Ferrebee, J. W., Ragan, Ch., Atchley, D. W., and Loeb, R. F.: Desoxycorticosterone Esters. Certain Effects in the Treatment of Addison's Disease, J. A. M. A. **113**: 1725, 1939.
25. Altschule, M. D., and Zamcheck, N.: Studies of the Circulation and Respiration in a Patient With Anasarca Following Administration of Cortin and Sodium Chloride, J. Clin. Endocrinol. **2**: 269, 1942.
26. Neuhaus, F.: Ueber die Bedeutung der Nebennierenadenome bei der Hypertonie, Beitr. z. path. Anat. u. z. allg. Path. **97**: 213, 1936.
27. Rinehart, J. F., Williams, O. O., and Capeller, W. S.: Adenomatous Hyperplasia of the Adrenal Cortex Associated With Essential Hypertension, Arch. Path. **32**: 169, 1941.
28. Kendall, E. C.: The Adrenal Cortex, Arch. Path. **32**: 474, 1941.
29. Raab, W.: The Presence and Chemical Determination of Adreno-Cortical (AC) Compounds in the Blood, Endocrinology **28**: 325-336, 1941.
30. Raab, W.: Adreno-Cortical Compounds in the Blood. Relation of Their Quantity to Adrenal Hypertension, Renal Insufficiency and Congestive Heart Failure, Arch. Int. Med. **68**: 713, 1941.
31. Kutschera-Aichbergen, H. v.: Ueber Herzschwäche, Berlin and Vienna, 1929, Urban & Schwarzenberg.
32. Westphal, K., and Sievert, C. M.: Ueber den Reizstoff der genuinen Hypertonie, Ztschr. f. klin. Med. **133**: 223, 1938.
33. Bennett, H. S.: Localization of Adrenal Cortical Hormones in the Adrenal Cortex of the Cat, Proc. Soc. Exper. Biol. & Med. **42**: 786, 1939.
34. Sjöstrand, T.: On the Capillary Circulation of Blood in the Suprarenal Body of Mice, Skandinav. Arch. f. Physiol. **71**: 85, 1934.
35. Kendall, E. C., Mason, H. L., McKenzie, B. F., Myers, C. S., and Koelsche, G. A.: Isolation in Crystalline Form of the Hormone Essential to Life From the Suprarenal Cortex, Proc. Staff Meet. Mayo Clin. **9**: 245, 1934.
36. Abelous, J. G., and Argaud, R.: The Formation of Adrenalin in the Suprarenal Gland. Role of Lipides and Lipoids in the Formation of Adrenalin, Compt. rend. Soc. de biol. **199**: 535, 1934.
37. Konschegg, T.: Adrenalin, Nebennieren und Blutdruck, Ztschr. f. d. ges. exper. Med. **81**: 559, 1932.
38. Koehler, A. E., and Eichelberger, L.: The Suprarenal Epinephrine-Lipoid Combination, J. Biol. Chem. **87**: 38, 1930.
39. Sanders, E.: Ueber die Wirkung von reinem Adrenalin und Nebennierenextrakten per os und am isolierten Organ, Arch. f. exper. Path. u. Pharmakol. **188**: 657, 1938.
40. Vesa, A.: Untersuchungen ueber die Einwirkungen des Adrenalins auf das Elektrokardiogramm, Acta Soc. Med. Fennicae "Duodecim," Helsinki, Ser. B. **26**: 5, 1939.
41. Thompson, W. O., and Heckel, N. J.: Male Sex Hormone, J. A. M. A. **113**: 2124, 1939.
42. Shambaugh, P., and Cutler, E. C.: Total Thyroidectomy in Angina Pectoris, AM. HEART J. **10**: 221, 1934.
43. Raab, W.: Roentgen Treatment of the Adrenal Glands in Angina Pectoris (One Hundred Cases), Ann. Int. Med. **14**: 688, 1940.
44. Raab, W.: Abnormal Adrenal Discharges in Angina Pectoris and Their Control Through X-Ray Therapy, J. Clin. Endocrinol. **1**: 977, 1941.
45. Davis, D., and Klainer, M. J.: Factors in the Production of Congestive Failure, AM. HEART J. **20**: 98, 1940.

THE aVL, aVR, AND aVF LEADS

A Simplification of Standard Lead Electrocardiography

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INTRODUCTION

STANDARD lead electrocardiograms, as Wilson, et al.,[1] have said, "may be regarded as a combination of two curves, each of which represents the potential variations during the cardiac cycle beneath a single electrode." In other words, the electrocardiograph, as routinely used, may be compared to a sphygmomanometer, which, instead of recording the actual systolic and diastolic levels of blood pressure, would merely indicate the difference between them (the pulse pressure). Because of this inherent defect, standard lead electrocardiography, despite its great value for almost forty years, has been limited. These limitations, in the main, are as follows:

1. Standard lead electrocardiograms are a composite of two equally important unipolar extremity leads[1] (the standard lead electrocardiogram is thus a bipolar extremity lead); whereas, in the case of precordial leads, the indifferent electrode records potentials which have but a minor influence on the electrocardiogram.

2. There is no constant relation between the direction of the deflection (upward or downward) and polarity. For example, an upward deflection in Lead I may represent five different combinations of polarity at that instant, namely,

a. (−) potential at right arm (+) at left arm
b. (−) potential at right arm (0) at left arm
c. (−) potential at right arm (−) at left arm, but more (+) than right arm
d. (0) potential at right arm (+) at left arm
e. (+) potential at right arm (+) at left arm, but more (+) than right arm

3. The standard leads are taken according to the convention of Einthoven,[2] and precordial leads according to that of the American Heart Association.[3]

4. Standard leads cannot be directly compared with precordial leads.

To obviate these limitations, the use of leads which represent the potentials derived from only one extremity was naturally suggested.[4a, b]

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Unfortunately, not much progress was made in this direction because of difficulties encountered in obtaining a simple indifferent electrode of zero potential. (Although the Wilson assembly[6] serves admirably, it is expensive and somewhat difficult to construct.) Fortunately, therefore, while studying extremity potentials, I was able to devise a very simple indifferent electrode of zero potential which can be constructed in the office in a few minutes.[5] Further, since unipolar extremity potentials, as ordinarily derived, are small in amplitude and difficult to analyze, I devised a technique of obtaining augmented unipolar extremity leads in order to obviate this defect.[5]

The system of electrocardiography described below consists, then, of the use of the three augmented unipolar extremity leads (the aV– leads) and a precordial lead, as follows:

1. The aVl lead*—the augmented left arm extremity lead.
2. The aVr lead—the augmented right arm extremity lead.
3. The aVf lead—the augmented left leg extremity lead.
4. The V_4 lead, in which the electrode is placed in the fifth intercostal space at the mid-clavicular line.

For purposes of investigation, however, we are using the regular series of precordial leads, namely, $V_{1 \text{ to } 6}$.[3]

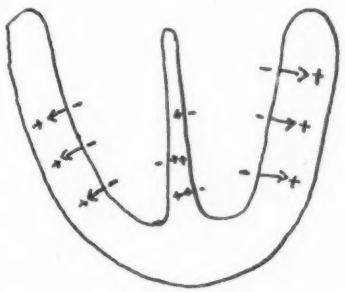

Fig. 1.—The spread of electrical activity in the ventricles. The arrows indicate the direction of spread, and the + and – signs, the relative polarities of the advancing wave of activity. The regression of electrical activity is *not* shown.

PHYSIOLOGIC PRINCIPLES UNDERLYING THE USE OF THE aV– LEADS

The potentials of the aV– leads vary directly with the electrical axis of the heart. This is true for both auricular and ventricular complexes. As a consequence, experimental observations on muscle strips and on the exposed heart are more or less directly applicable, as will be shown.

For our purposes in this paper, the following presentation of physiologic principles is adequate:

a. Function in a tissue (for example, heart muscle) is associated with the production of differences of electric potential.[7] Active muscle is relatively (–) to inactive muscle.

*The ordinary, unaugmented unipolar extremity leads are designated Vl, Vr, and Vf, respectively.[3]

b. No potential difference is produced by tissue within a zone of completely active, or completely inactive, muscle.[8a]

c. The electrical forces produced by the heart, therefore, are derived from a transition zone of muscle, either undergoing activation or returning to the resting state.[8a]

d. During activation, the side of the zone adjacent to the resting muscle elements (the direction in which the impulse is spreading) may be considered (+), and that adjacent to the active muscle elements as (–)[8a] (Fig. 1).

e. Further, in the heart the zone may be considered in relation to the endocardium or epicardium. If the electrode is placed "facing" the endocardium, i.e., within the chambers of the ventricles[8a] or over one of the large valvular orifices at the base of the heart, the potential will tend to be negative throughout the QRS complex, because the electrical impulse travels from within outward to the epicardium, and the endocardial surface remains relatively (–) to the epicardial[8a] (Fig. 1).

f. Similarly, potentials derived from the right upper extremity are normally (–) because "the attachment of the right upper extremity to the trunk lies opposite the large valvular orifices at the base of the heart so that the right arm displays variations in potential similar to those that occur in the ventricular cavity."[4b]

The aVr lead may therefore be considered as a quasi-intracardiac lead. In like manner, the precordial leads aVf and aVl (usually) may be considered quasi-extracardiac.

In this paper I have omitted discussion of the regression of electrical activity which produces the T wave.[8b, 9]

TERMINOLOGY AND GENERAL REMARKS

The leads are always taken so that positivity is represented by an upstroke in the record. All measurements should be made in terms of millimeters, NOT millivolts. (In the aV– leads 1.5 cm. = 1 mv., whereas in the precordial leads, 1 cm. = 1 mv., although in both instances the galvanometer is standardized in the same way.[5]) (Fig. 2.)

P, T, and U waves are described as usual.

For the QRS complex the following situation holds: It must be emphasized that the QRS complex is a single entity, and that the only reason for separate identification of the individual waves is for purposes of description. With this in mind, I have complied with the desire of the American Heart Association to have a standard nomenclature applicable to all leads:

a. QS = an initial (–) downward deflection, if not followed by an upward deflection.

b. Q = an initial (−) downward deflection, if followed by an upward deflection.

c. R = the first upward (+) deflection.

d. S = a downward (−) deflection, if present, following R.

e. R′ and R″ = additional upward (+) deflections after the first R.

f. S′ and S″ = additional downward (−) deflections after the first S.

To describe the relative sizes of the waves in a pattern, use small and capital letters, as, rS Qr, etc. (Fig. 2.)

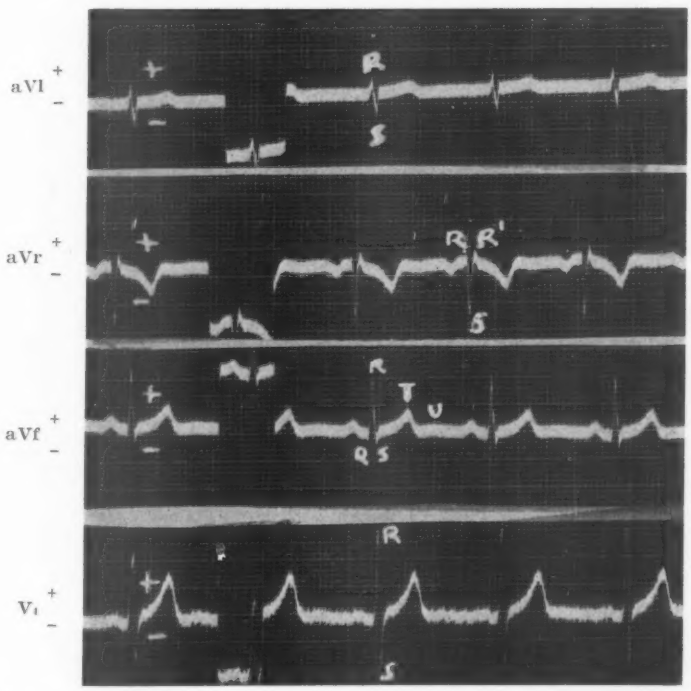

Fig. 2.—Normal male, aged 28 years. In both aV- and precordial leads the standardization mark rises or falls 1 cm.[5]

NORMAL RECORDS

Normal values for the amplitudes of individual waves are presented in Table I. The mathematical relations between standard and unipolar extremity leads are shown in Appendix A. In Fig. 2 a normal record is shown.

The aVl lead.—Unlike the aVr or the aVf leads, there is no basic normal pattern for any of the waves. P, though usually (+), may be (−). The main ventricular deflection and T are usually (+). Occasionally the aVl lead resembles the aVr lead and QRS and T are (−) (Fig. 3*a*).

The aVr lead.—There is a basic normal pattern of the aVr lead, consisting of a (–) P; a monophasic (–) QS; an isoelectric RS-T interval; and a (–) T (Fig. 2). Either R or both R and R′ may be present (Fig. 3*b*).

The aVf lead.—The basic pattern of the aVf lead is just the reverse of the aVr lead; there are a (+) P; a monophasic (+) QRS, comprising only an R; and a (+) T. Either Q or S, or both, may be present (Fig. 3*c*).

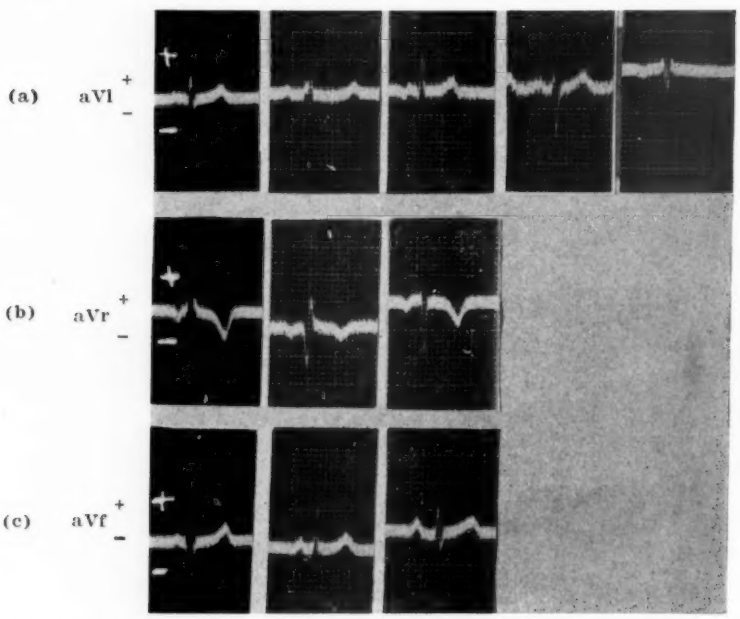

Fig. 3.—Examples of normal variations in the aV– leads. Each of the eleven records is from a different case.

AURICULAR PATTERNS

As was previously mentioned, the potential (shape) of the P wave in the aV– leads varies directly with the electrical axis of the auricular muscle. Since in the auricle the electrical axis corresponds closely to the actual path of the spread of the impulse, the shape of the P wave in the aV– leads offers a good clue as to the actual path of the impulse.

This is well illustrated in the case of auricular flutter. Although in standard leads the flutter waves appear to be composed of a short, followed by a long, stroke,[10] the fact that the impulse travels clockwise over a 360° path has long been well established.[10] If the aV– leads are used and the electrical axis for one complete auricular cycle is calculated, it will be seen that the pattern in auricular flutter is a modification of a sine curve (Fig. 4). Similarly, nodal rhythm, ectopic auricular impulses, etc., may be analyzed.

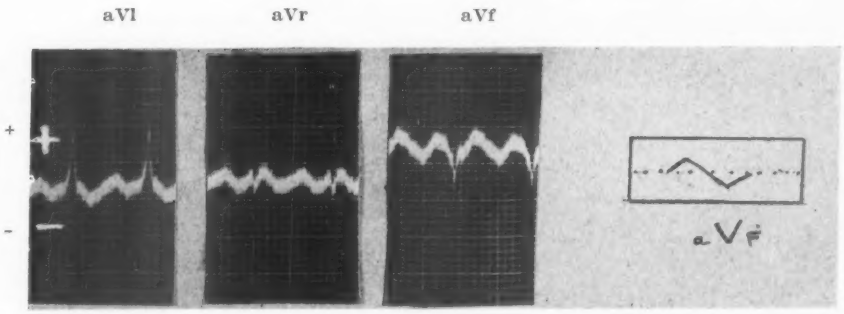

Fig. 4.—Auricular flutter. The small box at the right shows one complete auricular cycle in the aVf lead. It should be pointed out that, since there is a "circus movement" in operation, the points representing the beginning and end of the cycle are arbitrary. The presence of a deep Q in the aVf lead indicates myocardial damage.

VENTRICULAR PATTERNS

Without attempting to cover the entire field of electrocardiography, the basic patterns in axis deviation and ventricular hypertrophy, acute myocardial infarction, coronary insufficiency, pericarditis, and pulmonary embolism, and the electrocardiographic changes caused by the administration of digitalis will be described briefly.

Axis Deviation and Ventricular Hypertrophy.—It may be stated as axiomatic that the potentials of the aVl, aVr, and aVf leads are functions of the electrical axis of the heart, and further, that the algebraic sum of the potentials of these three leads, at a given instant, always equals zero. This is graphically illustrated in Fig. 5. The diagonal

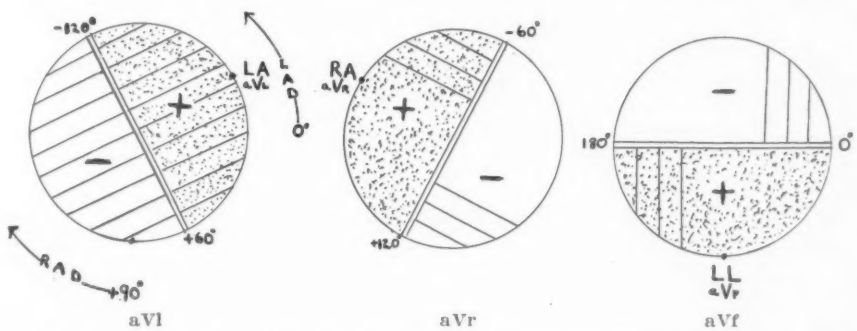

Fig. 5.—Graphs illustrating the relationships between the potentials and polarities of unipolar extremity leads and the electrical axis.

The diagonal and vertical lines indicate how the amplitudes of the records vary. In the diagrams, not all of the oblique and vertical lines were drawn.

In the aVl lead when angle α changes from +59° to +61°, the polarity of the auricular or ventricular deflection becomes – instead of +, and vice versa; when angle α changes from –119° to –121°, the polarity of the auricular or ventricular deflection becomes + instead of –, and vice versa.

In the aVr lead when angle α changes from –59° to –61°, the polarity of the auricular or ventricular deflection becomes + instead of –, and vice versa; when angle α changes from +119° to +121°, the polarity of the auricular or ventricular deflection becomes – instead of +, and vice versa.

In the aVf lead when angle α changes from +1° to –1°, the polarity of the auricular or ventricular deflection becomes – instead of +, and vice versa; when angle α changes from –179° to +179°, the polarity of the auricular or ventricular deflection becomes + instead of –, and vice versa.

and vertical lines illustrate how the QRS complex becomes larger or smaller with changes in the electrical axis.

With respect to axis deviation, by definition, left axis deviation exists when Einthoven's angle α passes 0° and becomes (−); and right axis deviation, when the angle α passes +90° in a clockwise fashion and becomes more (+).

To consider Fig. 5 for a moment again. Although the potentials of all three unipolar extremity leads vary with the electrical axis, the aVl lead seems to show these variations best, because as 0° is passed counterclockwise, the (+) potentials tend to increase in amplitude; and as +90° is passed clockwise, the (−) potentials tend to be augmented. The use of the left arm lead as a measure of axis deviation, however, is not original with me; Wilson, et al.,[6] and Kossmann and Johnston[4b] previously suggested it. *Therefore, as a general rule, an upward aVl lead potential represents left axis deviation; and a downward main aVl deflection, right axis deviation.*

In the event that it is desired to calculate the actual angle of the electrical axis of the heart (Einthoven's angle α), it will be necessary to make use of special tables which I compiled but which are omitted in this paper.

The Electrocardiographic Patterns of Left Axis Deviation and Left Ventricular Hypertrophy.—The patterns have arbitrarily been divided into four types, 1°, 2°, 3°, and 4°. From the graphs in Fig. 5, one would expect the first sign of left axis deviation to be a change in the polarity of the aVf lead from (+) to (−) (1°). Then, with increased axis deviation (2°), the aVr potentials should become increasingly smaller, until an angle of −60° is reached, when they should change and become (+).

In the aVl lead, left axis deviation should produce a heightened QRS until −30° is reached, when the potential should begin to decrease. Actually, this occurs (Fig. 6). However, when 2° left axis deviation becomes marked, signs of ventricular hypertrophy also appear (see below). The patterns of left axis deviation are described in Table II.

TABLE I

NORMAL VALUES IN THE aV– LEADS

	avl		avr		avf	
	MIN. (MM.)	MAX. (MM.)	MIN. (MM.)	MAX. (MM.)	MIN. (MM.)	MAX. (MM.)
P	−1	+1.5	−0.4	−2	0	+2.5
Q	0	−2	−2	−17	0	−3
R	+1	+10	0	+1.8	+1.2	+20
R′	0	+2	0	+4	0	+5
S	0	−8	0	−17	0	−6.8
S′	0	−2	--	--	0	−1.5
T	−1*	+1.5	−0.8	−3.5	0	+4
U	0	+0.5	0	−0.5	0	+0.5

*In the aVl lead, a (−) T is to be considered normal only if an rS pattern exists, or if the major QRS deflection is (−) so that the ventricular complex resembles that of the aVr lead.

Left Ventricular Hypertrophy.—With ventricular hypertrophy, unlike axis deviation, T-wave changes appear, and T points in a direction opposite to that of the main ventricular complex.

With the left ventricular hypertrophy, concomitant right ventricular hypertrophy may also occur, and the resultant electrical axis may approach normal, but the T-wave changes will be present.

Considering the QRS patterns, Barnes[12] has described two types of electrocardiographic patterns in cases of hypertensive cardiovascular disease, under the title "Chronic Left Heart Strain." In one, Lead II is similar to Lead I (Fig. 6*d*); in the other, Lead II is similar to Lead III (Fig. 6*e*). In the unipolar extremity leads, the main point of difference between these two patterns is in the aVr lead. When Leads II and I are similar, the main aVr deflection is deeply (−); in the type in which Leads II and III are similar, the main aVr potential has become (+).

TABLE II

THE ELECTROCARDIOGRAPHIC PATTERNS OF LEFT AXIS DEVIATION AND VENTRICULAR HYPERTROPHY

		1° LAD	2° LAD	3° LVH	4° LVH
		Angle α near 0°	Angle α (−)	Angle α less (−) than −60°	Angle α more (−) than −60°
aVl	QRS	+ :q may be present	Same as 1°	+ :q may be present	Same as 3°
	T	+		−	
aVr	QRS	−	Same as 1°	−	QR
	T	−		+	−
aVf	QRS	rsr or rsr's'	rS	rS	Same as 3°
	T	+	+	+	

TABLE III

THE ELECTROCARDIOGRAPHIC PATTERNS OF RIGHT AXIS DEVIATION AND VENTRICULAR HYPERTROPHY

		1° RAD	2° RVH	3° RVH
		Angle α more (+) than 90°	Angle α less (+) than +120°	Angle α more (+) than +120°
aVl	QRS	−:rS	−:rS	Same as 2°
	T	+ may be (−)	+	
aVr	P	−	Often large and notched	Same as 2°
	QRS	−	−	QR
	T	−	+	−
aVf	P	+	Often large and notched	Same as 2°
	QRS	+ :q may be present	+	
	T	+	−	

From Fig. 5 we learn that when the angle α passes from −59° to −61°, the potential at the aVr lead changes from (−) to (+). The value for angle α in Fig. 6*d* is −5°,* and in Fig. 6*e*, −70°.* In other words, Fig.

*By actual calculation.

6*e* represents merely a greater degree of axis deviation than Fig. 6*d*. The characteristics of these types are described in Table II.

Still another type of electrocardiographic pattern is found in certain cases of ventricular hypertrophy. Some of the features of left ventricular hypertrophy, and some which are attributable to right ventricular hypertrophy, are seen (Fig. 9*a*).

Right Axis Deviation and Right Ventricular Hypertrophy.—These patterns have been divided into three types, 1°, 2°, and 3°. Study of Fig. 5 reveals that an increase of right axis deviation will produce larger (–) aVl potentials. In the aVr lead, the amplitude of the (–) deflections should decrease until +120° is reached, when the main deflection becomes (+). In the aVf lead, the main deflection is always (+) (Fig. 6).

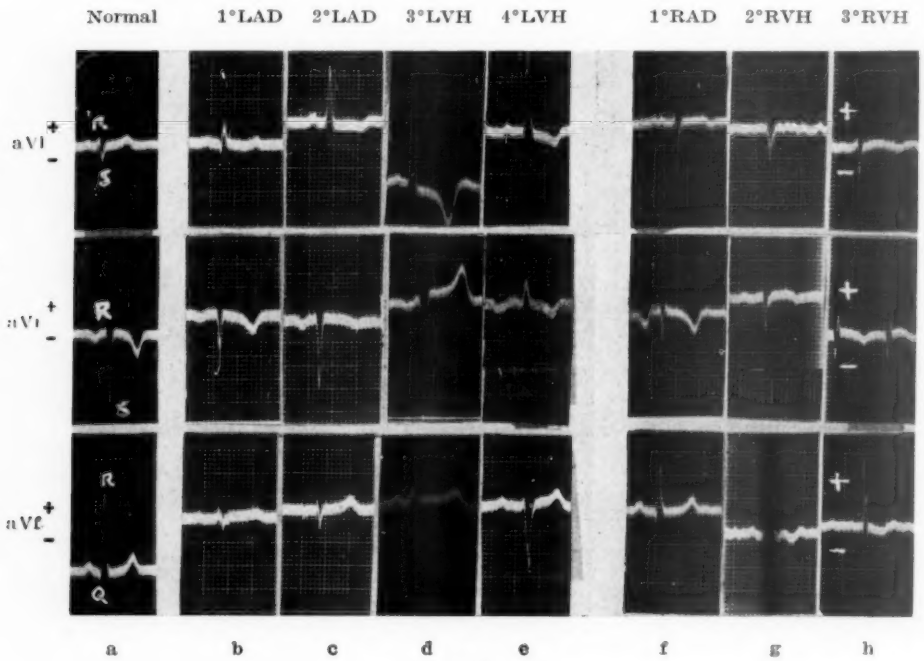

Fig. 6.

Fig. 6.—Electrocardiographic patterns of axis deviation and ventricular hypertrophy. *a*, Normal; *b*, left axis deviation 1°; *c*, left axis deviation 2°, the (–)T aVl is indicative of some degree of ventricular hypertrophy; *d*, left ventricular hypertrophy 3°; *e*, left ventricular hypertrophy 4°; *f*, right axis deviation 1°; *g*, right ventricular hypertrophy 2°: auricular fibrillation; *h*, right ventricular hypertrophy 3°: auricular fibrillation.

Right Ventricular Hypertrophy.—Here, again, Barnes[12] has described two types, one in which Leads I and II are similar (Fig. 6*g*), and another in which Leads II and III are similar (Fig. 6*h*).

In the unipolar extremity leads, again the main point of difference is in the aVr lead, and is caused by the degree of axis deviation. Fig. 6*g* represents an almost normal angle *a* (this is due in part to concomitant

left ventricular hypertrophy and rotation of the heart around its longitudinal axis). In Fig. 6*h* there is marked axis deviation.

The characteristics of right axis deviation and ventricular hypertrophy are presented in Table III.

Acute Myocardial Infarction.—When one of the coronary vessels is occluded, tissue anoxemia and death occur, and certain physiologic changes take place, irrespective of the location of the infarct.

First, a current of injury is produced. This is *not* observed in the electrocardiogram because its effect is neutralized during standardization (Fig. 7).

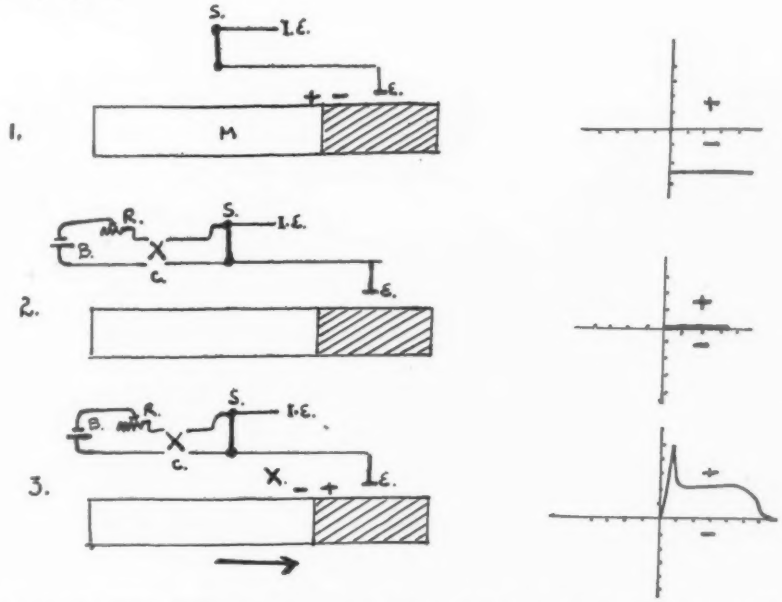

Fig. 7.—Diagram showing how current of injury is neutralized. *E*, Electrode; *I.E.*, indifferent electrode; *M*, strip of muscle immersed in a medium of uniform and extensive conductivity; *S*, galvanometer string; shaded area represents injured (or dead) muscle; + or − signs represent polarity as impressed on the string; *C*, current reverser; *B*, battery; *R*, variable resistance; arrow indicates direction of spread of impulse. *1*, Shows current of injury; *2*, shows how current of injury is neutralized with a battery, variable resistance and current reversing switch; *3*, shows type of electrogram obtained by passage of an impulse through the muscle strip from left to right. An electrode at x would record a (−) RS-T deviation.

Second, there are RS-T changes, for the following reason: as the electrical impulse enters the dying and dead area, the excitation wave is blocked because it cannot penetrate the injured tissue. The potential difference at this boundary between vital and injured tissue is, therefore, the cause of the RS-T segment deviations (Fig. 7). Whether the RS-T deviation will be (+) or (−) depends solely on the relation of the electrode to the infarcted area. *A unipolar lead which overlies or faces the infarcted region will record a* (+) *RS-T deviation; one which faces the normal surrounding tissue, a* (−) *RS-T deviation* (Fig. 7).

Third, T-wave changes occur as a later phenomenon. The T wave develops in a direction opposite to that of the RS-T deviation, and

occurs coincident with the regression of the RS-T deviation. (The reason for this will be described elsewhere.)[9]

Fourth, Q waves may also develop coincident with the RS-T deviations *in leads overlying or facing the infarct,* for the following reason: Normally as the excitation wave spreads out toward the epicardium, the precordial electrode faces the oncoming impulse and the initial deflection will be (+) (see Fig. 1). With infarction, there is no impulse, and an electrode overlying the infarct may be considered as facing the endocardium whose potential is (−). Thus, the initial deflection is (−), or a Q wave. It is as if a hole were cut in the ventricular wall and the electrode were placed over it.

In considering the subject of anterior and posterior infarcts, it should be emphasized that it is the location of the infarcted area, *not* the particular artery which has been thrombosed, that determines the electrocardiographic pattern.

Anterior Infarcts.—With infarcts of this type, the regions affected may include the anterior portion of the left ventricle, the adjacent portion of the interventricular septum, and the apex.[12]

The electrocardiogram in a typical case is illustrated in Fig. 8. The outstanding features of this pattern are:

aVl lead	QRS: A deep Q (which is the cause of the Q_1 of standard leads) and a prominent final R are present
	RS-T: +
	T: Later becomes (−) as the RS-T deviation regresses
aVr lead	QRS: Normal; occasionally a final R or R′ may appear
	RS-T: (−), usually inconspicuous
	T: (+)
aVf lead	QRS: Normal
	RS-T: (−)
	T: (+)

There is a reciprocal relation between the RS-T deviations and the T waves of the aVl and aVf leads. Precordial leads are described in Fig. 8. The explanation for these patterns is as follows: Precordial leads and the aVl lead overlie or face the infarct, which involves the anterolateral wall of the left ventricle,[15] and so record an initial (−) deflection, the Q, and a (+) RS-T. A Q (aVl), therefore, is more significant than a Q_1. The aVr and aVf leads, facing the surrounding vital tissue, record a (−) RS-T, and QRS is essentially normal.

It may be pointed out that, if a small area is infarcted, an electrode placed directly over the infarcted zone will record normal deflections up to the moment the impulse reaches the infarct and becomes blocked, causing the RS-T deviation. However, if the experimental infarct is made sufficiently large (as occurs in man), the initial (+) deflection disappears.[13b, 14]

When the anterior infarct is small or atypical, the standard leads may be equivocal or normal, and the only evidence may be present in the

aVl lead, in which the RS-T segment is characteristically flattened and T coved (Fig. 10*a*).[19]

Posterior Infarcts.—Electrocardiograms of this type are produced by infarction of a region which may include the posterior basal portion of the left ventricle and the adjacent portion of the interventricular septum.[12] This region, as Wilson has pointed out,[15] overlies the diaphragm and is *inferior* rather than *posterior*.

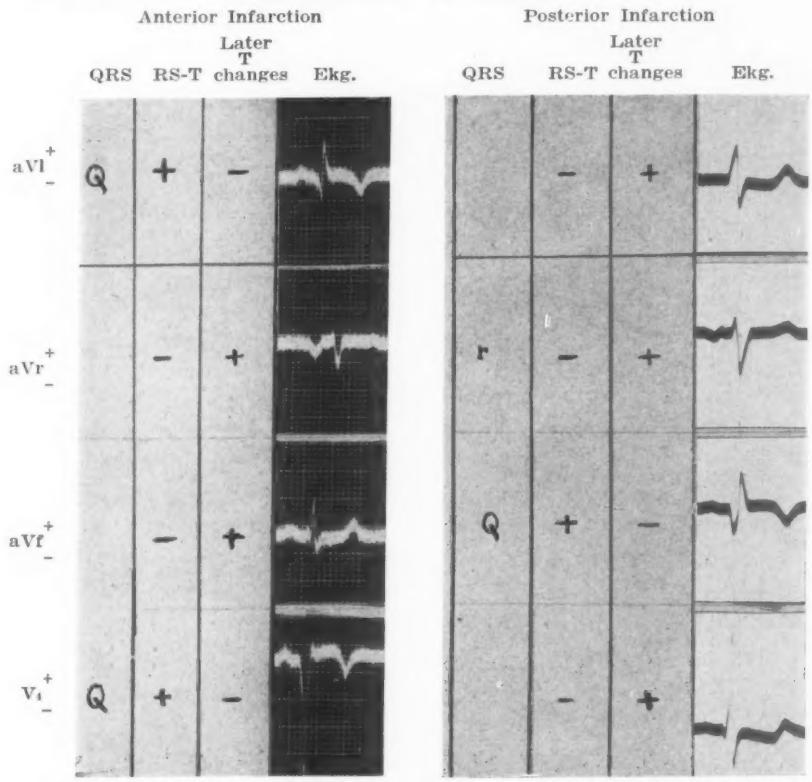

Fig. 8.—Typical electrocardiographic patterns observed in cases of acute myocardial infarction. The record of anterior infarction was taken on the tenth hospital day; that of the posterior infarction, two weeks after the attack.

A typical electrocardiogram is shown in Fig. 8. The significant features of this pattern are:

aVl lead QRS: Normal
RS-T: (−)
T: (+)

aVr lead QRS: Normal. An initial R* is often seen
RS-T: (−) inconspicuous
T: (+)

aVf lead QRS: Deep Q*
RS-T: (+)
T: (−)

*It is the Q of the aVf lead which is the cause of the Q_3. When present, the R of the aVr lead contributes to the Q_2. (Appendix A.)

As with anterior infarcts, there is a reciprocal relation between the RS-T deviations and T waves of the aVl and aVf leads.

Precordial leads are described in Fig. 8. When there is a small or atypical posterior infarct, standard leads may be normal, and the only evidence may be present in the aVf lead, which will show a small QRS with a Q and coronary T wave (Fig. 10*b*).[19]

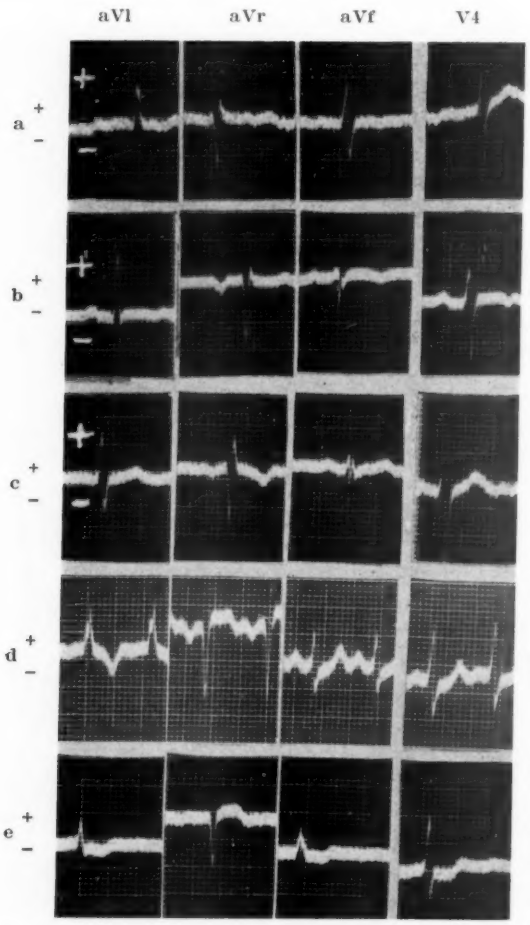

Fig. 9.—*a*, Atypical left ventricular hypertrophy, male, aged 44 years. Auricular fibrillation and digitalis effects. The deep S (aVf) makes the pattern atypical. *b*, Acute pericarditis (acute rheumatic fever), male, aged 32 years. Note the dome-shaped RS-T in the aVl, aVf, and V_4 leads. In the aVr lead, T is (+). *c*, Mild pulmonary embolism, male, aged 43 years. Four days after embolism. Standard leads showed an S_1 Q_3 pattern. *d*, Acute coronary insufficiency, female, aged 52 years. The patient died seven hours after record was taken, still in shock. The (−) T in the aVl lead is often observed. *e*, Digitalis effect, female, aged 63 years. Hyperthyroidism-auricular fibrillation.

Multiple Infarcts.—It is not always a simple matter to ascertain exactly what region has been infarcted for a variety of reasons. A new infarct may occur in a previously damaged heart, in which case electrocardiographic signs of the old infarct in the form of Q-wave changes

are often permanent. Again, the heart may be the seat of multiple, acute infarcts, in which case the reciprocal relations between aVl and aVf patterns are lost; or a complicating pericarditis may also obscure the picture.

Pericarditis.—There appears to be general agreement that the electrocardiographic changes in most instances of pericarditis are an expression of an associated subepicardial myocarditis.[16a, b] It is this, and *not* the presence of pericardial effusion, which is the cause of the RS-T segment deviation. A typical pattern is pictured in Fig. 9*b*.

The cause of the RS-T deviation is the same as in myocardial infarction. The damaged subepicardial tissue produces a slight block of the impulse. Leads from the surface of the heart, as the aVl lead, the aVf lead, and precordial leads, show, therefore, a (+) RS-T deviation and (–) T; and leads which "face" the endocardium, as the aVr lead, a (–) RS-T deviation and (+) T. These typical patterns are not always observed in all leads, however, depending on whether the pericarditis is localized or diffuse.

Acute Coronary Insufficiency.[19]—Acute coronary insufficiency provoked by a disproportion between the oxygen requirements of the heart and the coronary blood flow results in focal areas of myomalacia, largely subendocardial, without affecting the larger coronary arteries.[11] The electrocardiographic pattern, determined by the subendocardial localization of the muscle injury, is briefly as follows (Fig. 9*d*): The aVr lead, facing the injured endocardial area, records a (+) RS-T deviation. The aVl, aVf, and precordial leads, facing the surrounding vital tissue, record (–) RS-T deviations. Abnormal Q waves are not observed. The aVr lead normally presents a Q wave.

A similar pattern is often present during a seizure of angina pectoris due to acute, but temporary, myocardial ischemia. In cases of angina, I have also observed electrocardiographic evidence of myocardial damage in aV– leads, even at rest, when the standard leads were normal.[9]

Nonspecific Myocardial Injury.—Aside from coronary artery thrombosis and acute coronary insufficiency, there are a wide variety of conditions which may injure the myocardium, such as acute rheumatic fever, acute infectious diseases, severe anemia, and trauma. Without describing these in detail it may be stated that the location and extent of the injury, rather than the nature of the noxious agent, determine the electrocardiographic pattern.

Pulmonary Embolism.—"It would appear that the electrocardiographic pattern following pulmonary embolism is a classic example of changes due to unilateral (right) ventricular strain."[12] The changes observed, however, are variable,[17] and may include those pictured in Fig. 9*c*. In this record, the RS-T deviations which are so often seen did not occur. RS-T deviations, when present, are due to an associated

acute coronary insufficiency (see above). It may be observed that here the Q_3 is written by the aVl lead, *not* the aVf lead, as in myocardial infarction (Fig. 9*c*).

Digitalis Effects.[9]—The effects of digitalis on the electrocardiogram depend to a certain extent on the pattern prior to the administration of the drug. In general, the following changes occur in the ventricular complex of aV– leads:

1. A decreased Q-T or RS-T interval.
2. RS-T deviation in a direction opposite to that of the T wave.
3. Decrease in the amplitude of the T wave. When maximal, there are complete reversal of polarity and fusion with the RS-T segment (Fig. 9*e*). In this connection it should be borne in mind that RS-T deviations and T-wave changes may also be caused by adrenalin, insulin, and other drugs and functional conditions, such as postural hypotension.[18]

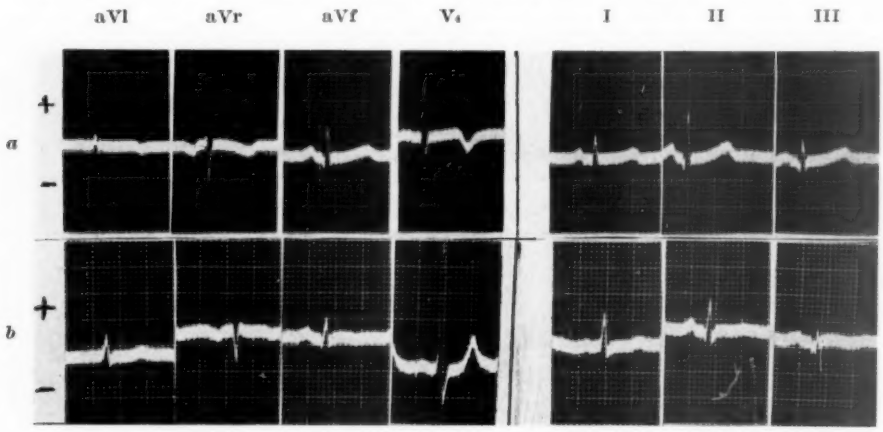

Fig. 10.—Atypical myocardial infarction. *a*, Anterior infarct, male, aged 41 years, two days after attack. Standard leads are normal. Lead V_4 is abnormal. The flattened RS-T and coronary T of the aVl lead are typical and characteristic. *b*, Posterior infarct, female, aged 53 years, one week after attack. Standard leads show equivocal T-wave changes. Lead V_4 is within normal. The q and coronary T of the aVf lead are characteristic of an atypical posterior infarct.

DISCUSSION

As with standard leads, the use of this system of "augmented" unipolar extremity leads is predicated on acceptance of the Einthoven triangle concept. Without going into a detailed discussion of the validity of this hypothesis, I will say that the fact that "augmented" unipolar extremity electrocardiograms may be obtained with either my or Wilson's indifferent electrode is, for practical purposes, proof of the applicability of this concept. Further, the calculation of the angle *a* in standard leads is dependent on this very concept.

Justification for the introduction of a "new" system of electrocardiography (if justification is necessary) is that the system I have presented is NOT new in the sense that the principles underlying its use

are identical with those governing standard leads. In fact, I might go so far as to say that the standard leads, rather than the unipolar extremity leads, were originally used because no technique existed in Einthoven's time by which a standard lead potential could be separated into its two component unipolar extremity lead potentials. It cannot be too strongly emphasized that a standard lead represents a combination of the potentials of two unipolar extremity leads,[1] and *not* the converse.

CONCLUSIONS

The outstanding features of the aVl, aVr, and aVf leads are as follows:

1. Since they are essentially unipolar extremity leads, they record potentials from only one region of the body, unlike the standard leads, each of which represents the combined potentials of two unipolar extremity leads.

2. In fact, the relation between the augmented unipolar extremity leads and standard leads is fixed, and may be expressed mathematically (Appendix A).

3. Positivity and negativity have definite significance when correlated with the actual electrical phenomena in the heart for both the aV– leads and the precordial V– leads. Further, in accordance with mathematical principles, positivity is always represented by an upward deflection.

4. The aVl, aVr, and aVf leads are so related that the algebraic sum of their potentials (at the same instant) equals zero.

5. Each of the aV– leads may be interpreted in relation to the others, or to precordial, esophageal, or any leads taken with an indifferent electrode of zero potential.

6. The potentials of the aV– leads vary directly with the electrical axis of the heart.

7. Since the same electrical phenomena produce unipolar extremity and bipolar standard leads, the patterns that have in the past been described in the standard leads may now be seen and analyzed in a clearer, uncombined form. In fact, the standard leads must be considered as complicated unipolar extremity leads.

8. An important clinical advantage of augmented unipolar extremity leads over standard leads lies in the diagnosis of coronary artery disease. For example, in a case of myocardial infarction, when the standard leads are normal, characteristic RS-T deviations and T-wave changes will occur in one or more of the aV– leads. Also, in angina pectoris, at rest, evidence of myocardial damage may be observed in aV– leads even when the standard leads are normal.

In the preceding pages I have in a broad and general way described the physiologic bases for the more important electrocardiographic

patterns, and their direct application to the aVl, aVr, and aVf leads, both normal and abnormal. With these leads, the patterns not only of the normal electrocardiogram, but also of axis deviation and ventricular hypertrophy, assume a logical sequence for the first time. This is to be expected, inasmuch as the QRS patterns are direct functions of the electrical axis.

In this system, the physiology of the RS-T segment deviations which have been previously described in acute myocardial infarction[13a] becomes directly applicable, which is impossible with standard leads. The same holds for the RS-T patterns of pericarditis, angina pectoris, coronary insufficiency, and pulmonary embolism.

Again, the full significance of Q_1, and especially Q_3, becomes apparent when these deflections are analyzed as component parts of unipolar extremity leads.

Although I did not elaborate upon it in this paper, the effects of digitalis on the RS-T segment and the T wave may be shown to follow a logical sequence, not only in the unipolar extremity leads, but also in precordial leads.[9]

However, the final word has not been written, either on the relation of the aV– leads to electrocardiographic physiology, or on their multifold patterns and interpretation. Many problems await solution; but I will say that study and use of these leads, especially at first, in conjunction with standard leads, will lead to a fuller understanding of not only standard leads and of the aV– leads and precordial leads, but also of the physiologic principles underlying electrocardiographic patterns.

Finally, the fund of knowledge that has been accumulated with the standard leads will NOT be lost with the use of this technique; rather, in transcribing it in terms of the aV– leads (using the equations in Appendix A), a more rational concept of the significance of this knowledge may be obtained.

I wish to express my appreciation to Dr. Frank N. Wilson, Ann Arbor, Mich., for his many helpful suggestions on terminology, and on the preparation of this paper; Doctors Leander H. Shearer, Frederick H. Howard, and Harry Greisman, of the Department of Medicine, and Dr. Alexander W. Kruger, Medical Superintendent, and Dr. Marcus Schramm, for their cooperation; and to the many others on the interne and nursing staff of the Lincoln Hospital, who so kindly assisted me in obtaining and selecting material.

APPENDIX A

Relationship of Augmented Unipolar Extremity and Standard Leads.—The value of potentials at the right arm, in terms of standard lead potentials, may be expressed by the equation:

$$RA = -\frac{I + II}{3} \qquad 6 \qquad 1$$

In the above equation, it is simpler to consider an upward deflection in the standard leads as (+), and a downward deflection as (–). For this reason, Lead I will

have to be considered as LA minus RA, and Lead II as LL minus RA. (The reason for this is that, in Lead I, both a (–) potential of RA and a (+) potential of LA produce an upward deflection; and similarly, in Lead II, both (–) RA and (+) LL potentials produce an upward deflection. In Lead III an upward deflection is produced by (–) LA and (+) LL potentials.

Equation 1 may, therefore, be rewritten:

$$RA = -\frac{(LA-RA) + (LL-RA)}{3} \qquad 2$$

or

$$= -\frac{LA + LL - 2RA}{3} \qquad 3$$

Now RA + LA + LL = 0[1]
Therefore, LA + LL = –RA
and equation 3 becomes:

$$RA = -\frac{-RA - 2RA}{3}$$

$$= -\frac{-3RA}{3}$$

$$= RA$$

Since the aVr lead 3/2 RA[5]
equation 1 becomes:

$$aVr = -\frac{I + II}{2}$$

Similarly,

$$aVl = \frac{I - III}{2}$$

and

$$aVf = \frac{II + III}{2}$$

REFERENCES

1. Wilson, F. N., Macleod, A. G., Barker, P. S.: The Potential Variations Produced by the Heart at the Apices of Einthoven's Triangle, Am. Heart J. **7**: 207, 1931.
2. Einthoven, W.: Weiteres über das Elektrokardiogramm, Pflüger's Arch. f. d. ges. Physiol. **122**: 517, 1908.
3. American Heart Association, Am. Heart J. **15**: 107, 235, 1938.
4. a. Eckey, P., and Frölich, P.: Zur Frage der unipolaren Ableitung des Elektrokardiogramms, Arch. f. Kreislaufforsch. **2**: 349, 1938.
   b. Kossmann, C. E., and Johnston F. D.: The Precordial Electrocardiogram. I. The Potential Variations of the Precordium and of the Extremities in Normal Subjects, Am. Heart J. **10**: 925, 1933.
5. Goldberger, Emanuel: A Simple, Indifferent, Electrocardiographic Electrode of Zero Potential and A Technique of Obtaining Augmented, Unipolar, Extremity Leads, Am. Heart J. **23**: 483, 1942.
6. Wilson, F. N., Macleod, A. G., Johnston F. D., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, Am. Heart J. **9**: 447, 1933.
7. a. Bernstein, J.: Zur elektrochemischen Grundlage der bioelektrischen Potentials, Biochem. Ztschr. **50**: 393, 1913.
   b. Bayliss, W. M.: Principles of General Physiology, ed. 2, New York, 1918, Longmans, Green & Co., pp. 645-650.
   c. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Distribution of the Action Currents Produced by Heart Muscle and Other Excitable Tissues Immersed in Extensive Conducting Media, J. Gen. Physiol. **16**: 423, 1932.
8. a. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Interpretation of the Initial Deflection of the Ventricular Complex of the Electrocardiogram, Am. Heart J. **6**: 637, 1931.

b. Macleod, A. G.: The Electrogram of Cardiac Muscle: An Analysis Which Explains the Regression or T Deflection, AM. HEART J. **15**: 165, 1938.
9. To be published.
10. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, Shaw and Sons, London, 1925.
11. Master, A. M., Gubner, R., Dock, S., and Jaffe, H. L.: Differentiation of Acute Coronary Insufficiency With Myocardial Infarction From Coronary Occlusion, Arch. Int. Med. **67**: 647, 1941.
12. Barnes, A. R.: Electrocardiographic Patterns, Springfield, Ill., 1940, C. C Thomas.
13.a. Wilson, F. N., Johnston, F. D., and Hill, I. G. W.: The Interpretation of the Galvanometric Curves Obtained When One Electrode Is Distant From the Heart and the Other Near or in Contact With the Ventricular Surface. II. Observations on the Mammalian Heart, AM. HEART J. **10**: 176, 1934.
b. Wilson, F. N., et al.: The Electrogram in Myocardial Infarction With Particular Reference to the Initial Deflection of the Ventricular Complex, Heart **16**: 155, 1933.
14. Bellet S., and Johnson, C. G.: The Effect of Coronary Occlusion Upon the Initial Phase of the Ventricular Complex in Precordial Leads, J. Clin. Investigation **13**: 725, 1934.
15. Wilson, F. N.: in Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, 1936, The Macmillan Co.
16.a. Bellet, S., and McMillan, T. M.: Electrocardiographic Patterns in Acute Pericarditis: Evolution: Causes and Diagnostic Significance of Patterns in Limb and Chest Leads: A Study of 57 Cases, Arch. Int. Med. **61**: 381, 1938.
b. Noth, P., and Barnes, A. R.: Electrocardiographic Changes Associated With Pericarditis, Arch. Int. Med. **65**: 291, 1940.
17. Sokolow, M., Katz, L. N., and Muscovitz, A. N.: The Electrocardiogram in Pulmonary Embolism, AM. HEART J. **19**: 166, 1940.
18. Nordenfelt, O.: Über functionelle Veränderungen der P- und T-Zacken im Elektrokardiogramm, Acta med. Scandinav. Suppl. **119**: 1941.
19. Goldberger, Emanuel: The Use and Advantage of Augmented Unipolar Extremity Leads (aV-Leads) in the Electrocardiographic Diagnosis of Myocardial Infarction (Coronary Thrombosis) and Acute Coronary Insufficiency, New York State J. M., in press.

TREATMENT OF EDEMA WITH AN ORALLY ADMINISTERED MERCURIAL DIURETIC

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ST. PAUL, MINN.

IN THE treatment of many patients with edema, mercurial diuretics are today regarded as indispensable. There have been a number of successive compounds, each of which possessed distinct advantages over its predecessor, but all have had the disadvantage of requiring parenteral administration. This usually necessitated intravenous injections often enough to maintain an edema-free state. Minor, but uncomfortable, toxic effects have occurred frequently, especially in older people. It was found that these could be avoided by giving smaller and more frequent doses. Obviously this is a definite drawback from the economic aspect, and also predisposes to thrombosis of the veins, which is a disadvantage when medication must be carried out over a considerable time. These facts stress the importance of securing an effective preparation for oral administration.

The most satisfactory diuretics of this series have been markedly improved, with increased effectiveness and lessened toxicity, by combining them with theophylline. It has been shown by Chrometzka,[1] Saxl,[2] and Görl[3] that this combination can be safely and effectively used by mouth. Batterman, DeGraff, and Rose[4] reported on the use of an oral preparation in comparison with an intravenous preparation of the same material. They used an arbitrary dose for twenty-nine patients at variable intervals over a relatively short period, and reported that the preparation was safe and effective. Blackford[5] reported favorable results in four cases.

This report is concerned with the use of oral tablets of a complex mercury compound, sodium salicyllallylamide-o-acetate, in part a chemical combination, in part a mixture, with theophylline (salyrgan-theophylline tablets). They have been used over a period of twenty months in a series of thirty-nine patients. Twelve were hospital patients, fourteen were patients in an outpatient cardiac clinic, and thirteen were ambulatory private patients. Most of them had long been under care for chronic myocardial insufficiency, and had received various diuretics.

METHOD

Patients with edema associated with the diseases listed in Table I were treated. Those with cardiac disease had heart failure, and were receiving therapeutic doses of digitalis. All of the patients received 6 Gm. of ammonium nitrate daily, start-

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ing at least two days before the administration of the salyrgan-theophylline tablets was begun. No other medication was used except sedatives, as indicated. Hospital patients were kept strictly in bed. Intake and output records were kept in many cases, but, on the whole, proved much less reliable in estimating the results of diuresis than weighing the patients daily under constant conditions. This was done before breakfast, after emptying the bladder, with the patient wearing the same clothing, and using the same scales. Only those patients who had maintained a constant weight for several days were included. The preparation used was an investigational product of salyrgan-theophylline in the form of tablets for oral administration (STO). Each tablet contained 0.08 Gm. of salyrgan and 0.04 Gm. of theophylline. This represented 0.03168 Gm. of mercury per tablet.

TABLE I

DIAGNOSIS	NO.	RESULTS			TOXIC EFFECTS
		GOOD	FAIR	NONE	
Mitral Stenosis	8	5	1	2	2
Hypertension	14	10	3	1	6
Coronary Sclerosis	8	7	0	1	3
Cirrhosis of the Liver	3	2	0	1	1
Aortic Stenosis	2	2	0	0	1
Syphilitic Aortitis	1	1	0	0	0
Phlebitis—Legs	1	0	1	0	0
Ca. Ovary	1	0	0	1	0
Ca. Rectum	1	1	0	0	1
Total	39	28	5	6	14

The results are recorded in Table II. "Good" includes those patients who obtained marked relief from their edema, as indicated by a persistent weight loss and increased urinary output. "Fair" includes a group of patients who, with the initial dose, lost no weight and had no significant increase in urinary output. These patients, however, did respond to intravenous injections of salyrgan-theophylline, after which the edema was prevented from recurring by the use of the STO tablets. "None" includes those who fell in neither of the previously described groups.

The urine and blood were watched for toxic effects, and the patients were carefully questioned about toxic subjective manifestations. Under the heading, "Initial Weight Loss," data are given to show the maximal diuretic effect of the tablets in terms of weight loss, and the time and number of tablets necessary to obtain it. "Total Time" indicates the length of the period of observation over which the salyrgan-theophylline was given, not necessarily continuously. "Total Tablets" shows the number of salyrgan-theophylline tablets which were used during the "Total Time."

OBSERVATIONS

Most of the patients had been previously under treatment for chronic myocardial insufficiency. They had been receiving various diuretics, but ammonium nitrate was the only diuretic used for several days prior to starting the STO tablets. This explains the relatively small weight losses which were recorded in most of the "good" results. Massive edema was infrequent; it occurred only in Cases 1 and 12 (hospital patients) and in Case 36. This was an ambulatory patient who had been discharged from the hospital one month previously and was becoming progressively more dyspneic. These all responded well to the tablets.

TABLE II

CASE NO.	SEX	AGE	RESULTS			INITIAL WT. LOSS			TOTAL DURATION	TOTAL NO. TAB.	TOXIC EFFECTS	DIAGNOSIS
			GOOD	FAIR	NONE	LBS.	DAYS	TAB. USED				
1.	F.	44	*			24	9	34	9 d.	34	0	Hypertension
2.	M.	71	*			12	6	48	8 m.	450	0	Cirrhosis of liver
3.	F.	40	*			5	1	5	16 m.	624	+	Hypertension
4.	M.	73	*			3	3	10	1 m.	80	0	Phlebitis—Legs
5.	F.	74		*		--	--	--	14 d.	68	+	Hypertension
6.	M.	67	*			17	20	50	15 m.	481	0	Syphilitic aortitis
7.	F.	51	*			7	8	12	5 w.	33	+	Mitral stenosis
8.	M.	64		*		--	--	--	3 m.	110	+	Hypertension
9.	F.	79	*			5	7	8	4 m.	112	0	Hypertension
10.	F.	62	*			4	5	18	2 w.	22	+	Hypertension
11.	M.	72	*			17	9	54	2 m.	98	0	Cor. dis.
12.	F.	42	*			25	8	43	6 w.	102	0	Aortic stenosis
13.	M.	50			*	--	--	--	3 d.	15	+	Mitral stenosis
14.	F.	53	*			6	11	30	3 m.	226	–	Cor. dis.
15.	F.	50	*			8	6	54	6 w.	175	–	Mitral stenosis
16.	M.	69	*			3	5	20	8 d.	20	–	Hypertension
17.	F.	59	*			16	14	112	12 m.	550	–	Mitral stenosis
18.	M.	46		*		--	--	--	6 w.	155	–	Mitral stenosis
19.	F.	45		*		--	--	--	2 w.	30	–	Hypertension
20.	M.	48	*			10	5	15	3 w.	25	–	Cor. dis.
21.	F.	54	*			Marked diuresis		30	6 w.	55	*	Cor. dis.
22.	F.	70			*	--	--	--	2 w.	21	–	Hypertension
23.	M.	80	*			8	14	35	9 w.	100	–	Hypertension
24.	F.	60	*			Marked diuresis		--	1 d.	6	–	Cor. dis.
25.	M.	56	*			3	1	5	1 d.	5	–	Cor. dis.
26.	M.	44	*			10	7	10	1 m.	25	*	Aortic stenosis
27.	M.	50			*	--	--	--	1 w.	10	–	Cirrhosis
28.	F.	60			*	--	--	--	1 d.	5	–	Ca. ovary
29.	M.	56	*			5	5	15	1 w.	15	*	Cor. dis.
30.	F.	75	*			Marked diuresis			3 w.	13	*	Ca. rectum
31.	M.	61			*	--	--	--	2 w.	20	*	Cor. dis.
32.	F.	53	*			7	5	8	1 w.	8	–	Mitral stenosis
33.	F.	53	*			10	5	20	22 w.	706	*	Hypertension
34.	M.	63	*			10	4	24	10 m.	250	–	Hypertension
35.	F.	69	*			8	12	48	5 m.	261	*	Hypertension
36.	M.	55	*			28	35	210	2 m.	282	–	Mitral stenosis
37.	M.	62	*			4	2	12	5 m.	98	*	Cirrhosis
38.	F.	64	*			--	--	--	4 d.	4	–	Hypertension
39.	M.	49			*	--	--	--	7 d.	42	–	Mitral stenosis
Total			29	4	6						14	

Age.—The patients ranged in age from forty to eighty years. There were eight between forty and fifty years, twelve between fifty and sixty years, eleven between sixty and seventy years, and eight between seventy and eighty years. This is shown in Table II, which gives the distribution of results and toxicity among the various age groups. The number is too small to be of value in drawing conclusions, but it appears that age plays no part in the results, and that no unusual risk is involved in giving the drug to elderly patients.

Sex.—Taking the edematous patients as they presented themselves, twenty women and nineteen men were given the tablets. As shown in Table II, there was no significant difference in the responses of the two sexes. The difference in toxic manifestations was not significant.

Dosage.—The first fifteen patients received a single dose, as has been the custom with the intravenous route. Usually this was five tablets, which is a total of 0.1584 Gm. of mercury, or approximately twice the amount (0.0792 Gm.) in the usual 2 c.c. intravenous dose of salyrgan theophylline. Of these patients, seven developed toxic symptoms, and six had no diuresis. It was then decided to give the tablets in varying and divided doses, in an attempt to learn the effective dose for each patient. One tablet was given after meals, and the dose was increased to the point of effective diuresis or the appearance of toxic effects. Satisfactory results rarely occurred with less than six tablets daily, and this was adopted as a safe starting dose. Occasionally as many as nine tablets daily were necessary for diuresis. Larger doses produced toxic effects.

Patients now have been given the tablets as long as sixteen months without objective or subjective evidence of toxicity. The total number of tablets taken varied greatly, as shown in Table II. Thirteen patients received a total of more than 100 tablets. In only one of them, Case 35, did toxic effects necessitate cessation of medication. There was no indication that prolonged administration was harmful; seventeen patients have used the tablets over a period of six weeks to twenty months.

Mode of Action.—When the drug was given in a fairly large single dose (as is done with the intravenous method), a successful result was marked by the appearance of diuresis in six to eight hours, persisting for about six hours. Some increase in urinary output persisted for twenty-four hours, and, occasionally, the effect lasted into the second day, but not longer. Patients who had been uncomfortable with such rapid diuresis from intravenous administration experienced the same discomfort when the tablets were given in a quantity sufficient to produce a comparable diuresis. However, many of this group of patients were able to take the tablets in divided daily doses without trouble. In these cases, the diuresis was much milder, appeared in twelve to twenty-four hours, and persisted while the tablets were being given and as long as any edema remained.

Diagnosis.—Table I shows the distribution of the patients, the therapeutic results, and the incidence of toxic effect, according to clinical diagnosis. There were twenty-two patients with degenerative heart disease (coronary sclerosis and hypertension), ten with rheumatic heart disease, three with hepatic cirrhosis, one with syphilitic aortitis, and one each with thrombophlebitis of the legs, carcinoma of the ovary with metastasis, and carcinoma of the rectum. (When multiple diagnoses were made, the predominating factor was used in this table.) From the table it appears that no particular etiologic group yielded a better clinical response to the STO tablets than other groups. However, a proportionally greater number of toxic effects occurred in the degenerative heart disease groups.

Results.—Table II shows that twenty-eight patients had good results from the STO tablets. It is of interest that ten of these are listed under "Toxic Effects." However, in only two of these was it necessary to discontinue medication, for the toxic effects were transitory. One of these was Case 30, a woman, aged seventy-four, who had carcinoma of the rectum, with severe nutritional anemia, associated with dyspnea. She was much improved by profuse diuresis, but severe abdominal colic made it inadvisable to continue the use of the drug. The other patient, Case 35, a woman, aged sixty-nine, was able early to take the tablets with less weakness and abdominal pain than when the intravenous route was used. Later the tablets were not well tolerated, and they were discontinued.

The "fair" results must be regarded as satisfactory, for in those cases it was possible to dispense with intravenous administration after initial diureis, which was the object desired.

Of the thirty-nine patients, the diuresis was unsatisfactory in only six. A brief résumé of these follows:

CASE 13.—Male, aged forty-two, with mitral stenosis and marked edema and ascites, had responded well to mercurial diuretics intravenously. He failed to have diuresis on five STO tablets daily for three days, after which they had to be discontinued on account of nausea and abdominal distress.

CASE 22.—Female, aged seventy, with hypertensive heart disease, was one of the early cases, and only three tablets every other day were given. No results were obtained over a period of three weeks; the medication was stopped, and the patient was not seen again.

CASE 23.—Male, aged fifty, with hepatic cirrhosis, was given two doses of five tablets, four days apart, with no effect.

CASE 28.—Female, aged sixty-six, with carcinoma of the ovary and ascites, was given only one dose of five tablets; no response was obtained.

CASE 31.—Male, aged sixty-one, with coronary sclerosis, was given three tablets daily to supplement weekly injections of 2 c.c. of salyrgan-theophylline. Patient continued to gain weight, and the drug had to be stopped because of toxicity.

CASE 39.—Male, aged forty-nine, with mitral stenosis. No diuresis was obtained after two weeks; the patient received six tablets daily.

Only one of these failures (Case 31) was definitely the result of intolerance to the drug. Others might have been, but the trials were unsatisfactory because none were given further treatment after a rest, and none had received the maximum number of tablets which were often necessary to produce diuresis.

Toxic Effects.—No evidence of kidney irritation or blood disturbance was found. Nausea, vomiting, diarrhea, abdominal discomfort and pain, and general weakness were the toxic effects which were noted. In general, these were not severe. One or more occurred in fourteen patients. In half of these the effects were transitory, and the medication continued. In four the tablets were not given again because the patients remained free of edema. In three cases the use of STO tablets was

discontinued because of recurring abdominal discomfort and diarrhea on repeated trials. A brief discussion of the symptoms and their significance follows:

Nausea occurred seven times. In three patients it was mild, occurred only with the early doses, and further medication was continued. In four patients the medication was stopped. Two of these patients were unable to resume it, and two were not given a further trial. Nausea was twice associated with vomiting, once in each case, and was a minor incident.

Diarrhea occurred six times. In Case 3, in which the patient is still under treatment, it occurs about once a week. The tablets are then stopped for twenty-four hours, the diarrhea ceases, and the medication is resumed. In Case 7 the patient had three loose defecations after each dose of three tablets, given every two days; medication was not interrupted. In Case 26 the patient had several loose movements after single doses of five tablets; the medication was continued. In Case 30 the patient had many loose movements, associated with pain, on taking one tablet twice daily. Medication was stopped. In Case 31 the patient had two to four watery movements, associated with marked abdominal distress, after two tablets daily; medication was discontinued. In Case 35 the patient had two watery stools after a dose of two tablets. Marked discomfort made it necessary to stop medication.

Abdominal pain, in the form of colicky, cramp-like discomfort, occurred in three cases. In Case 21 the patient received eleven doses of five tablets each over a period of six weeks; she had severe pain with the first dose, but none thereafter. In Case 30 the patient had severe pains after each dose of two or three tablets, and had to discontinue them. In Case 5 the patient had marked pain after the first two doses of three each, but none subsequently. The pain is distinguished from abdominal discomfort by its severity and acuteness. Discomfort is not uncommon when one asks about it, but only four patients volunteered the complaint. It was not sufficient to indicate stopping the tablets.

Many patients who are receiving effective doses of mercurial diuretics intravenously complain of marked general weakness for about twenty-four hours after the administration. This has also occurred three times in this series. In Case 3 it was quite marked after five-tablet doses, and did not occur when divided daily doses of three to six tablets were given. In Case 35 the patient complained of weakness regardless of the mode of administration. In Case 37 the patient had this symptom with early doses, but gradually overcame the tendency.

In general, it may be said that the toxic effects were usually not severe, that they were often transitory, and that they showed no tendency to affect vital functions. In most instances they did not prevent further effective use of the tablets. Diarrhea is the most likely of all the toxic symptoms to make it impossible to use the drug.

DISCUSSION

At this stage of the study it appears that two STO tablets three times a day is the best method of starting the drug, and is a dose which will be tolerated well generally. With this dosage one may expect enough diuresis to cause a weight loss of one to eight pounds daily; the effect is most pronounced in those patients who have the greatest amount of edema, and diminishes as the edema becomes less. When the edema has disappeared and no further weight loss occurs, the dose of STO tablets was reduced to an amount necessary to prevent reaccumulation of fluid. Frequently it has been possible, after a period of time, meanwhile keeping the patient's activities within the limits permitted by his cardiac reserve, to discontinue the tablets without recurrence of the edema. In these cases it was occasionally necessary to continue the ammonium nitrate, but not always. In Cases 6 and 8 it was possible to discontinue the STO tablets for several weeks at a time before recurring edema, associated with overexertion, necessitated resumption of the treatment. It can be stated definitely that divided daily doses, varying in size according to the need for diuresis, and maintained at a level sufficient to prevent the accumulation of edema, constitute the most satisfactory method of using the tablets.

The variable response of some patients to intravenous administration also occurs with oral administration. In Case 2 the patient failed to show diuresis on six tablets daily for three weeks, but, after an interval of four months, good diuresis was obtained, with a weight loss of fourteen pounds; his status was maintained without STO tablets after they had been stopped two months later. In Case 23 the patient, on five tablets every other day, had no diuresis for one month, then lost ten pounds in two weeks. Thereafter his weight remained constant, and he showed marked clinical improvement without the mercurial. In Case 34 the patient, who has been under observation for ten months, has shown marked variability in his response. Over a period of several weeks no results were obtained from the STO, either in reducing the edema or maintaining freedom from edema. Sometimes the tablets would maintain a given weight after it had been reduced by intravenous administration, whereas, at others, a very satisfactory diuresis was effected by the STO tablets. On the whole the results in this case were considered satisfactory.

SUMMARY

Salyrgan-theophylline, in the form of enteric-coated tablets for oral administration, was used as a diuretic in thirty-nine patients.

Satisfactory diuresis occurred in twenty-nine patients.

Toxic effects were noted in fourteen patients, usually in the form of irritation of the colon, but these were seldom severe.

Experiences in ascertaining the ideal dosage are described, and a method of using the tablets is suggested.

REFERENCES

1. Chrometzka, F.: Die diuretische Wirkung peroral gegeben Salyrgans, Fortschr. d. Therap. **15**: 87, 1939.
2. Saxl, P.: Ueber perorale Novasuroltherapie, Wien. klin. Wchnschr. **39**: 816, 1926.
3. Görl, P.: Zur peroralen Salyrgan-Therapie, Med. Klin. **35**: 578, 1939.
4. Batterman, R. C., et al.: Treatment of Congestive Heart Failure With an Orally Administered Mercurial Diuretic, AM. HEART J. **21**: 98, 1941.
5. Blackford, L. M.: Salyrgan-Theophylline by Mouth, J. M. A. Georgia **29**: 397, 1940.

Clinical Reports

SUDDEN DEATH OF A RUGBY INTERNATIONAL AFTER A TEST GAME

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CASE REPORT

After having played a strenuous game at Johannesburg in July, 1940, S. C. L., 32 years of age, captain of the Transvaal Representative Rugby Team, collapsed and died.

Autopsy.—The body was that of an adult, European male, and was well built and muscular. Weight was 169 pounds; height, 6 feet. There was marked cyanosis of the face, neck, shoulders, and fingernails. No gross abnormalities of the central nervous system were detected. There were congestion of the vessels of the brain and marked engorgement of the veins on the surface.

Significant pathologic changes were found in the circulatory system. The heart was generally hypertrophied, and weighed 482 Gm. (17 ounces). The hypertrophy was most apparent in the left ventricle, the wall of which measured 2.7 cm. in thickness. There was dilatation of all of the cavities of the heart, especially of the right ventricle, which also showed hypertrophy. Its wall was 0.7 cm. thick. The papillary muscles were markedly thickened and prominent. Macroscopically, the myocardium appeared firm. However, numerous fibrotic patches were irregularly distributed in the left ventricle. The aortic valve was competent, although the cusps were slightly thickened. The mitral valve, which was also competent, admitted two fingers. On the surface of the mitral valve there was a large atheromatous patch.

The left coronary artery showed numerous atheromatous areas which had caused marked narrowing of the lumen at three places. One of these atheromatous areas was located at the orifice of the left coronary artery, and another at a point about midway along the anterior descending branch. Atheromatous patches were also present in the right coronary artery. The diameter of the ascending aorta and the aortic arch was normal, but the wall was extraordinarily soft and thin. The descending aorta measured a little over half an inch in diameter, which is less than half the normal size. There were many atheromatous patches in various parts of the intima.

There was congestion of the thoracic and abdominal organs. The trachea and bronchi contained thick mucopus. The lungs were slightly emphysematous and showed some edema and a slight excess of pigmentation. The hilar nodes were considerably enlarged.

The liver was congested, but otherwise normal; it weighed 2,495 Gm. (5½ pounds). There was considerable congestion of the spleen, and it was enlarged (weight, 454 Gm.); on section it showed a marked excess of lymphoid tissue.

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The left kidney was very small (weight, 62 Gm.), and was the seat of advanced hydronephrosis. The parenchyma was stretched and thinned, and the pelvis was much dilated. The left ureter was sharply kinked about one inch above the bladder. The right kidney was greatly hypertrophied (weight, 330 Gm.).

There was a persistent thymus gland which weighed 26 Gm. (normal weight at this age, 15 Gm., according to Wolf[1] and Cowdry[2]). The genital organs were conspicuously small.

Microscopic Examination.—There were several areas of fibrosis in the heart muscle. The papillary muscles and the base of the left ventricle were especially affected. Areas of narrowing of the coronary arteries showed marked atheromatous thickening. The intima was greatly distorted. Atheromatous changes were also found in the aorta. The thymus gland contained scattered foci of entirely normal thymus tissue embedded in fatty tissue; there were areas of considerable infiltration and several large collections of lymphocytes. Numerous Hassall's corpuscles of large size were observed. The blood supply of the gland was abundant. The entire picture was that of an active gland, rather than the involutionary structure which one would expect at the age of 32 years (Aschoff[3]). Sections of the left kidney revealed normal tissue, although there was extreme congestion. The right kidney showed chronic pyelitis, fibrous thickening of the capsule, patchy fibrosis, and infiltration of the parenchyma with small round cells. All lymphoid structures were hyperplastic, including those of the throat, nasopharynx, intestinal canal, and the lymph nodes.

Previous History.—L. had been one of the most prominent South African rugby players of the preceding decade. He was known as "the iron man of rugby." He had represented his country on the playing fields of South Africa, Britain, Australia, and New Zealand. His identical twin brother J. also died during exertion at the age of 30 years. J. was bathing in the water at the coast when he suddenly collapsed and was swept away. The following information was kindly supplied by Major Danie Craven, captain of the Springbok team:

"I have known L. since 1931, and played on the same team with him on numerous occasions. During 1937 and 1938, I traveled with him to Australia and New Zealand, and roomed with him at various places. I always regarded L. as a very ill man. He used to complain of severe pain in the lower portion of his back. This pain he thought was due to kidney trouble. On many occasions I had to massage his back because of these pains. He also suffered from boils. After every football match he felt sick. He used to put his finger into his throat until he vomited, after which he felt better. He could not take any alcoholic drinks because they also made him sick. His stamina was exceptionally good. However, in the course of the Australia-New Zealand tour, two years prior to his death, his efficiency deteriorated greatly. During the last matches of the tour his performance was very poor. His strength was outstanding, and on the boat he performed wrestling matches with the strongest of his teammates. He always had a husky voice, and suffered from chronic bronchitis. When he was tired, as, for example, after a game, he breathed heavily and noisily. He smoked at least thirty cigarettes a day.

"His twin brother J., whom I also knew very well, was apparently an identical twin. J. looked the same as L., had the same husky voice, and played the same type of game as his brother. In 1937, J. went swimming at Port Elizabeth inside the fenced portion of the beach. It was a quiet day and the water looked like a lake. After a few minutes of bathing, J. suddenly collapsed and sank. His body was never found."

Very little information is available concerning L.'s condition immediately prior to his death. It could be ascertained, however, that, between February and July, 1940, he lost more than 20 pounds in weight. This may have indicated failing health. A roentgenogram of his chest which was taken a few months before he

died (anteroposterior; distance, 5 feet; standing) does not show as much cardiac hypertrophy as was present at autopsy. Unfortunately, no lateral roentgenogram was made.

DISCUSSION

This is a case in which a congenital developmental abnormality caused a fatal circulatory crisis in a first-class athlete. There are many remarkable features. First of all, the deceased's twin brother had died two years before, also during exertion. Unfortunately, post-mortem examination in this instance was not possible; otherwise it is more than likely that an attempt could have been made to prevent the second catastrophe. Second, study of this case emphasizes the truth of the statement made on previous occasions[4, 5] that even an extraordinarily high standard of physical efficiency is not at all a reliable indicator of the state of health of the athlete concerned. The outstanding performances of L. were possible in spite of a grossly abnormal circulatory system.

The probable development of the disease and mechanism of death may be as follows:

Development of Disease.—Persistence of the thymus gland arrested the normal puberty and postpuberty development of the circulatory system. This arrest of growth, which also affected the urogenital system, caused the descending aorta to remain in an infantile state. Consequently, the heart was compelled to pump against a greatly increased resistance. It may be assumed that the arterial blood pressure was high. Hypertrophy and dilatation of the heart followed. The lymphatic tissue throughout the body was more active than usual and the spleen was greatly enlarged.

The early development of atheromatosis can be interpreted as a result of the extraordinary hydrodynamic strain upon blood vessel walls, a strain which, under the pathologic circumstances, was aggravated by strenuous physical activities.

The heart had to work under most unfavorable conditions, and the multiple fibrotic patches in the myocardium bear witness to the deficiencies of blood supply. It is remarkable that, with such a circulatory system, the man had been capable of such outstanding physical performances. As similar observations have been communicated by one of us (Jokl[4, 6]) on several previous occasions, it may now be accepted as an established fact that there is no strict relationship between heart disease and even an outstandingly high exercise tolerance.

Mechanism of Death.—The mechanism of death in this case seems clear. The deceased had taken part in a strenuous game. The oxygen requirements of his heart were thus greatly increased. After the game he took a hot bath. This must have shifted large amounts of blood from the intestinal circulation into the skin. In combination with the physiologic fall of blood pressure after the exercise, this must have added to the existing deficiency of blood supply to the coronary artery. The

significance of such physiologic phases in the causation of the final collapse of a diseased circulation has recently been demonstrated by Blumgart, Schlesinger, and Davis.[7] Furthermore, we have evidence that there were accumulation and stasis of inflammatory exudate in the hydronephrotic right kidney, which caused contractions of the smooth muscle of the renal pelvis and ureter. It is probable that unphysiologic tension in intestinal cavities elicits, by means of a reflex, spastic contraction of the coronary arteries. This has been proved conclusively for the stomach.[8] The autopsy also revealed signs of infection of the respiratory tract. This must have caused a further impairment of the functional efficiency of the heart.

In 1844, Rokitansky[9] drew attention to the simultaneous occurrence in adults of an infantile aorta, hypertrophy of the heart, and underdevelopment of the genital system. Although it has been assumed for a long time that the thymus gland exerts a direct influence on puberty and postpuberty development, it is only now that a more detailed picture can be drawn. We are especially indebted to Timme,[10] whose studies made possible a full understanding of the condition known as status thymicolymphaticus. Timme showed that the effects of persistence of the thymus gland, leading to arrest of development, mostly at puberty, are often compensated by hyperfunction of other glands in the body. The primary abnormalities caused by thymic persistence are lymphoid hyperplasia, gonadal and adrenal deficiency, a low blood sugar level, low blood pressure, and hypoplasia of the heart and vessels. In most cases, marked compensatory efforts of the organism lead after some time to a profound change in the picture.

The suprarenal cortex and the pituitary are strongly stimulated. We have asked ourselves whether the high standard of physical efficiency of this rugby player could perhaps be explained partly by a special compensatory effort of the suprarenal cortex. The changes in the heart were clearly the result of an attempt on the part of the circulatory system to overcome the obstacle created by the underdevelopment of the descending aorta.

Wolf[1] states that one of the three possible causes of death in cases of status thymicolymphaticus is weakness of the muscular coat of the arteries which renders them incapable of withstanding sudden changes in blood pressure. This would apply in our case.

In view of the circumstances under which the sudden death of L. and his twin brother occurred, Wolf's suggestion that swimming and bathing should be forbidden to people suffering from status thymicolymphaticus appears to be well founded.

SUMMARY

Summarizing, it appears that death occurred because of sudden coronary insufficiency. There was narrowing of the coronary artery

caused by atheromatosis. There was the physiologic fall of blood pressure after the exercise. Large amounts of blood were shifted into the skin as a result of taking a hot bath. The oxygen requirements of the heart muscle were greatly increased after the exercise. It is probable that reflex spasm of the coronary artery was caused by the frustrated efforts of the diseased right kidney to expel its inflammatory contents. It may be assumed that permeability of the myocardial cell membranes was adversely affected by the concurrent infection of the respiratory system.

This observation allows a detailed analysis of a case of status thymicolymphaticus, a term which has in the past often been used in a rather general way. We can trace the history of the patient back to the persistence of the thymus gland after puberty. We can thus understand the arresting effect of this primary developmental disturbance upon the maturation of the descending aorta. This latter anatomic deficiency explains the secondary pathologic reactions which created the above described extraordinary situation and caused death.

REFERENCES

1. Wolf, W.: Endocrinology in Modern Practice, Philadelphia and London, 1939.
2. Cowdry, E. V.: Problems of Ageing. Biological and Medical Aspects, London, 1939.
   Cowdry, E. V.: Textbook of Histology, London, 1938.
3. Aschoff, L.: Pathologische Anatomie, Jena, 1923, Vol. II, p. 173 (H. Schridde, Thymus).
4. Jokl, E., and Melzer, L.: Acute Fatal Non-traumatic Collapse During Work and Sport, South African, J. M. Sc. **5**: 4, 1940.
5. Jokl, E., and Suzman, M.: Aortic Regurgitation and Mitral Stenosis in Marathon Runner, J. A. M. A. **114**: 467, 1940.
6. Jokl, E.: Zusammenbrüche beim Sport, Vienna, 1935.
   Jokl, E., and Parade: Zur Frage der Beurteilung von Herzfällen in der sportärztlichen Praxis, Med. klin. No. 32, 1933.
7. Blumgart, H. L., Schlesinger, M. J., and Davis, D.: Studies on the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis, and Myocardial Infarction to the Pathologic Findings, Am. Heart J. **19**: 1, 1940.
8. Bergmann, E.v.: Functionelle Pathologie, Berlin, 1936, p. 113.
9. Rokitansky, C.: Handbuch der allgemeinen Pathologischen Anatomie, Vienna, 1844, Braumüller und Seidel, Vol. II, p. 585.
10. Timme.
11. Goldzieher, M. A.: The Endocrine Glands, New York and London, 1939.

TEMPORAL ARTERITIS

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TEMPORAL arteritis, an unusual and new syndrome, was first described by Horton, Magath, and Brown,[1] in 1934. Since that time, only a few similar cases have been reported. A patient with this disease who was treated on the Sanders oscillating bed is reported in this paper.

CASE REPORT

A white woman, aged 62 years, was first seen at her home because of excruciating pain in the right temporal region, fever, sweats, dizziness, gastric distress, and general malaise. Approximately three weeks previously, the patient complained of a mild unilateral headache which could not be relieved with the ordinary sedatives. This was soon followed by fever, sweats, and general malaise. During the preceding week, dizziness, gastric distress, and vomiting were added to the list of complaints. Her past history was essentially negative. Because of the grave condition of the patient and the severity of her symptoms, she was admitted to the hospital.

Physical examination revealed a swelling which extended upward for approximately 2½ inches from the right temporomandibular joint. The surrounding skin was moderately hyperemic. The right temporal artery was very prominent, tortuous, thickened, and tender. There were no palpable nodules. Pulsations were absent in the right temporal artery, but present in the left. There was a rather marked hyperesthesia of the entire right side of the scalp. The pupils were contracted and equal. The pupils were dilated with a mydriatic and the eyes examined on several occasions by Dr. Morris Simpson. A slight opacity of the right lens was found, but the vessels were normal and there was no evidence of choking of the discs. The ears, nose, and throat appeared normal. No lymph node enlargement was found. The lungs and heart were essentially negative. The blood pressure was 155/80. No organs could be palpated on abdominal examination. The reflexes were slightly hyperactive. The temperature ranged from 99° to 101° F. The pulse rate varied from 98 to 124.

The hemoglobin was 89 per cent, the erythrocyte count, 4,630,000, and the leucocyte count, 9,750. The differential leucocyte count showed 91 per cent polymorphonuclear cells (filamented, 81 per cent, nonfilamented, 10 per cent) and 9 per cent lymphocytes. The color index was 0.9. The blood Wassermann reaction was negative. There was no nitrogen retention in the blood, and the blood culture was negative. The urine was normal. The spinal fluid was clear and colorless. It gave positive Pandy and Ross-Jones tests, and the colloidal gold curve was 4444444321. The spinal fluid Wassermann reaction was negative. There was no pleocytosis.

The patient's condition became progressively worse. The headache was unbearable and could not be controlled with ½ gr. of morphine intramuscularly. She appeared desperately ill, did not respond very well, and her speech became slurred. Finally, the patient became delirious, and the possibility of brain tumor with increased intracranial pressure was considered. Dr. Frank Teachnor was called in

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consultation. However, the neurologic examination was essentially negative, except for a suggestively positive Babinski and Chaddock on the left. On later and repeated examinations, the Babinski and Chaddock were found to be definitely negative. Roentgenologic examination of the head revealed increased vascular markings in the left frontal area, limited to the inner table, high in the vertical plane of the left frontal area. There was no evidence of tumor or increased intracranial tension. The sella turcica appeared normal.

On entering the hospital, the patient received 50 c.c. of a 50 per cent glucose solution intravenously, ½ gr. of morphine intramuscularly, an ice cap to the head, and a 1-2-3 enema; the head of the bed was elevated. However, the patient did not obtain any appreciable relief until 2 gr. of sodium luminal were given intramuscularly. On awakening, the symptoms were as severe as ever. Cibalgin tablets were given by mouth without results. Finally, the patient was put on the Sanders oscillating bed, and enjoyed her first symptomless and natural sleep without any medication. She showed remarkable improvement on the bed and was dismissed from the hospital in ten days. The patient remained on the bed at home for the next six weeks, oscillating the bed twenty-four hours a day for the first four weeks, and approximately fifteen hours a day for the last two weeks. She made a remarkable recovery, appears alert, and is entirely free from symptoms. The swelling above the right temporomandibular joint receded, and the surrounding skin is normal in appearance. Although pulsations have returned, the right temporal artery is still a little thickened. Up to January 2, 1941, none of the old symptoms have returned. The final diagnosis of temporal arteritis was made entirely from the clinical manifestations. The close resemblance of this localized condition to that in other cases which have been reported justifies the above diagnosis.

COMMENT

Little is known of this new type of localized arteritis, and the etiology and pathologic criteria are not as yet established. In the cases which have been reported, the only relief from symptoms was obtained by resection of the involved portion of the temporal vessel. Since the oscillating bed has been used with such success in the treatment of peripheral vascular diseases, we felt justified in trying it for this new peripheral vascular syndrome. The result exceeded our expectations.

SUMMARY

A case of temporal arteritis is reported. The patient was successfully treated on the Sanders oscillating bed.

REFERENCE

1. Horton, B. T., Magath, T. B., and Brown, G. E.: Arch. Int. Med. 53: 400, 1934.

THE ELECTROCARDIOGRAM IN TRAUMATIC PERICARDITIS

Case Report

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THE value of electrocardiographic changes after injury of the heart by stab or gunshot wounds of the chest has been definitely established.[1-5] Previously the alterations of the S-T segment and T wave were ascribed either to direct damage to the myocardium, or to coronary artery injury, or to ligation of a coronary vessel, with subsequent infarction of the myocardium. The diffuse pericarditis which is invariably present in cases of injury of the heart may explain the discrepancy between the electrocardiographic pattern and that of myocardial infarction alone. Diffuse pericarditis has a distinct electrocardiographic pattern of its own.[4, 6-10]

The following report of a pericardial stab wound is presented because it clearly demonstrates the role which diffuse pericarditis plays in causing electrocardiographic abnormalities. In this case there was neither gross myocardial involvement nor any coronary vessel damage. This was demonstrated during the operation which was undertaken to stop hemorrhage from the lacerated pericardium, lung, and chest wall.

CASE REPORT

M. J., a 30-year-old colored woman, was brought into the emergency room of Michael Reese Hospital on the night of Oct. 15, 1939. She had sustained a stab wound of the left anterior chest wall about 5 inches long, centered below the nipple, and extending upward and outward toward the axilla. The wound was bleeding profusely. A quarter of a grain of morphine was given hypodermically, and an intravenous infusion of physiologic saline solution was begun. Consciousness was at a low enough ebb to permit exploration of the wound without giving her an anesthetic. The entire chest wall had been opened, with complete transsection of the fifth rib. Several bleeding vessels were clamped and the wound was spread, exposing the lung and pericardium. There was bleeding from a laceration in the lung about an inch long. This was quickly controlled by sutures. There was a tear in the pericardium near the base of the heart about an inch in length, with venous bleeding that was controlled by several ligatures. The myocardium was found to be uninjured, and there was little free blood in the pericardial sac. The pericardium was loosely sutured to prevent pleurocardial adhesions. Several hundred cubic centimeters of blood were left in the pleural cavity, and the chest wall was quickly closed with interrupted catgut sutures in the muscle and fascia, and silk in the skin. The closure was airtight.

From the Cardiovascular and Surgical Depts., Michael Reese Hospital.
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The blood pressure was now only 80/60 mm. Hg. The pulse rate was 120, and the quality of the pulse was poor. Respiration was increased, but not embarrassed. The patient was given acacia solution and human serum intravenously, and two hours later the blood pressure was 130/98, the pulse rate, 96, and the patient had regained consciousness.

The next morning her general condition remained fairly good. The right border of the heart was percussed 2 cm. to the right of the sternum. The entire left hemithorax was dull, and the breath sounds were suppressed over the upper lobe and absent over the lower. The erythrocyte count was 2,800,000 and the hemoglobin, 40 per cent.

Improvement was gradual until October 20. Dyspnea occurred occasionally and was always relieved by morphine. Roentgenograms of the chest confirmed the diagnosis of massive hydropneumothorax. At no time were there any clinical signs of cardiac tamponade. A pericardial friction rub was first heard October 20. On October 21 thoracentesis was performed because of the severe dyspnea, and 450 c.c. of blood were removed, leaving a positive pleural pressure. After this procedure, the pulse rate fell from 140 to 120 and the respirations from 38 to 30 per minute, and there was considerable subjective improvement.

On October 23 the temperature rose to 102.6° F. rectally, and the pericardial friction rub was more pronounced. Because of recurrent respiratory distress, the patient was placed in an oxygen tent and improved greatly. Oxygen therapy was discontinued October 26. Thereafter improvement was gradual, though slow. The wound healing was primary, and the sutures were removed on the thirteenth day. The only complication was abdominal distress and vomiting on several occasions; this was controlled by a dry diet. The lung re-expanded slowly; roentgenograms showed about 50 per cent collapse on November 1. On November 21 the patient was sent to a convalescent home. On December 13 a roentgenogram showed complete aeration of the upper lobe and only a barely recognizable amount of fluid in the lower part of the chest. The temperature remained normal after November 7.

COMMENT

This patient's electrocardiograms (Fig. 1) showed the changes which are expected in diffuse pericarditis. No significant QRS changes occurred. There was a concordant elevation of the S-T segment in the limb leads on October 23, and this was replaced by T inversion in all the limb leads on November 6 which waned and eventually disappeared. At the same time QRS was entirely up in Lead CF_2; inversion of the T waves appeared in the chest leads on November 6, and waned and disappeared in subsequent records. These mutations and the time of their evolution are not characteristic of myocardial infarction, but are typical of diffuse pericarditis of other than traumatic origin.

The electrocardiograms in this case failed to show any of the characteristic QRS changes in any of the leads or the discordant deviation of the S-T segment and the T wave in Leads I and III which occurs in the usual case of recent myocardial infarction. A local area of myocardial necrosis of traumatic origin would be expected to produce one of the classical patterns of recent myocardial infarction, provided it was properly located. This occurs because patients who have traumatic necrosis

rarely have any preceding cardiac disease. Therefore, the absence of a characteristic coronary contour may be taken as evidence against the presence of massive necrosis of the myocardium. Obviously, if diffuse pericarditis complicates massive necrosis of the myocardium, a composite electrocardiographic pattern may be expected.

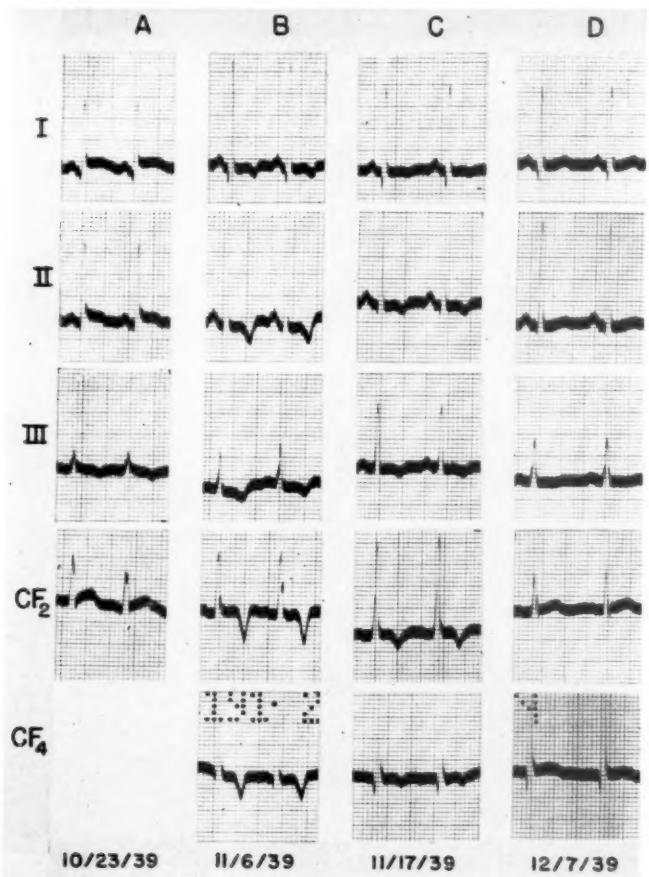

Fig. 1.

A correct interpretation of the mechanism which is responsible for the electrocardiographic changes is important in considering the prognosis in cases of traumatic heart involvement. This may also become important from a medicolegal standpoint. Histologic examination of the heart in cases of diffuse pericarditis has shown that the inflammatory process is confined to the uppermost layers of the myocardium.[11, 12] Because of this, the amount of myocardial damage is much more restricted than would be the case if the myocardium had been traumatized or the coronary circulation interfered with. Although myocarditis secondary to diffuse pericarditis may lower the functional capacity of the heart, it

does so to a lesser extent than localized massive necrosis of the heart muscle. Recognition of the peculiar type of electrocardiographic change which diffuse pericarditis can produce helps to distinguish this condition from myocardial infarction.

This case, which is unique as far as we can ascertain, presented the opportunity to make a complete electrocardiographic study of traumatic diffuse pericarditis, unassociated with myocardial damage other than that which the pericarditis itself causes in the subepicardial layers. It therefore helps to establish clearly the peculiar contour which diffuse pericarditis produces in the electrocardiogram, and lends experimental support to the view that there is a particular electrocardiographic pattern in diffuse pericarditis. In this human experiment there was no complicating factor which could disturb the electrocardiographic picture, although the temporary pericardial effusion and the acute hemorrhage and shock may have altered the abnormalities in the first record. However, the steady evolution of the electrocardiographic changes over a period of six weeks makes it unlikely that these factors played any considerable role. The evidence seems clear from the examination at the time of operation that the myocardium and the coronary vessels were not affected.

This experience raises a question as to the extent to which diffuse pericarditis in other cases of stab and gunshot wounds of the chest was responsible for some of the electrocardiographic alterations that have been reported.

SUMMARY

A case of stab wound of the chest is reported, in which, at operation, which was done to stop bleeding, only a laceration of the parietal pericardium (and lungs) occurred, without trauma to the epicardium, myocardium, or coronary blood vessels. The opportunity of following the electrocardiographic changes in serial records was afforded. The clinical course and electrocardiographic pattern were those of traumatic diffuse pericarditis. A distinction is made between such electrocardiographic changes and those which occur after localized myocardial necrosis of traumatic origin.

We are grateful to Dr. L. N. Katz for his help in preparing this report.

REFERENCES

1. Davenport, G. L.: Suture of Wound of the Heart: Ligating the Interventricular Branch of the Left Coronary Artery and Vein, J. A. M. A. **82**: 1840, 1924.
2. Davenport, G. L., and Markle, P.: The Electrocardiogram in Stab Wounds of the Heart. A Case Report, J. Thoracic Surg. **3**: 374, 1934.
3. Davenport, G. L., Blumenthal, B., and Cantril, S.: Electrocardiographic Studies of a Stab Wound of the Heart, J. Thoracic Surg. **5**: 208, 1935.
4. Winternitz, M., and Langendorf, R.: Das Elektrokardiogramm der Perikarditis, Acta med. Scandinav. **94**: 141 and 274, 1938.
5. Noth, P. H., and Barnes, A. R.: Electrocardiographic Changes Associated With Pericarditis, Arch. Int. Med. **65**: 291, 1940.

6. Katz, L. N., Feil, H. S., and Scott, R. W.: The Electrocardiogram in Pericardial Effusion. II. Experimental, AM. HEART J. 5: 77, 1929.
Scott, R. W., Feil, H. S., and Katz, L. N.: The Electrocardiogram in Pericardial Effusion. I. Clinical, AM. HEART J. 5: 68, 1929.
7. Porte, D., and Pardee, H. E. B.: The Occurrence of the Coronary T-Wave in Rheumatic Pericarditis, AM. HEART J. 4: 584, 1929.
8. Barnes, A. R.: Electrocardiographic Pattern Observed Following Acute Coronary Occlusion Complicated by Pericarditis, AM. HEART J. 9: 734, 1934.
9. Schwab, E. H., and Herrmann, G.: Alterations of the Electrocardiogram in Diseases of the Pericardium, Arch. Int. Med. 55: 917, 1935.
10. Holzmann, M.: Elektrokardiographische Befunde bei Perikarditis, Ztschr. f. klin. Med. 128: 731, 1935.
11. Vander Veer, J. B., and Norris, R. F.: The Electrocardiographic Changes in Acute Pericarditis; a Clinical and Pathological Study, AM. HEART J. 14: 31, 1937.
12. Bellet, S., and McMillan, T. M.: Electrocardiographic Patterns in Acute Pericarditis; Evolution, Causes and Diagnostic Significance of Patterns in Limb and Chest Leads; a Study of Fifty-Seven Cases, Arch. Int. Med. 61: 381, 1938.

UNUSUAL SITE OF AN ANEURYSM OF THE AORTA

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ANEURYSMS originate most frequently from the ascending part of the aorta, and have a tendency to develop toward the right side. Distention and displacement of the aortic wall in this direction are favored by the minimum resistance offered by the lung, as well as by the fact that the right wall of the ascending aorta receives the greatest impact from the column of blood which is expelled during systole; for the outflow tract of the left ventricle runs an oblique course from low on the left to high on the right. Aortic aneurysms which arise from the ascending aorta and extend toward the left side of the chest are exceedingly rare, and create unusual clinical pictures which may cause considerable diagnostic difficulties.

CASE REPORT*

A 52-year-old white man had acquired syphilis at the age of 23. He had never had antisyphilitic treatment, except local applications. The Wassermann reaction was said to have been invariably negative. There were no other diseases.

Eight years earlier the patient started to have shortness of breath during severe effort, such as mountain climbing. Thereafter his condition remained unchanged for seven and one-half years, after which time a definite deterioration began to take place. Shortness of breath became more intense and occurred even on slight effort. A severe pressing and burning pain was simultaneously experienced in the precordium, with radiation to the back and down the left arm to the fingertips. Attacks of nocturnal dyspnea occurred several times, and were associated with rattling in the chest and expectoration of white, frothy sputum. During the preceding six months the patient had lost more than 16 pounds in weight. Recently the attacks of precordial pain had become more frequent and occurred even when the patient was at rest. He also complained of a persistent feeling of soreness in the precordial area. In November, 1931, he was admitted to the hospital.

The patient was of gracile body build and moderately well nourished. His face showed a slightly livid discoloration. There was no edema or ascites. A loud stridor was audible even when the patient was at rest. The slightest effort in bed caused marked dyspnea. No distinct pulsations were observed in the veins of the neck, and there were no dilated cutaneous veins on the chest. There was no difference in temperature, skin color, or pulse between the two halves of the body. The pupils were circular, equal in size, and reacted promptly to light and in accommodation. There was no tracheal tug.

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*The case was demonstrated by Dr. Stefan Feher at a meeting of the Society of Internal Medicine, in Vienna.

The percussion note was hyperresonant over the right lung. The left half of the diaphragm was at the level of the tenth rib, and did not descend with deep inspiration. The right half of the diaphragm was about 4 cm. below this level, and underwent normal inspiratory movement. Normal vesicular breathing was heard over the right lung, whereas breath sounds were barely audible over the left side.

The precordial region was prominent, and the skin over the precordium was edematous. The precordial bulge extended upward to the third and downward to the sixth rib; it extended from the left border of the sternum to the fourth intercostal space, 3 cm. beyond the left midclavicular line. The points of greatest convexity of the bulge, at the fourth and fifth ribs, were tender to palpation. There was a distinct pulsatory heaving of the prominent area during systole; this was most pronounced in the fourth intercostal space at the left mid-clavicular line (Fig. 1). The lower end of the sternum also showed a slight pulsation. No circumscribed apex beat was visible or palpable.

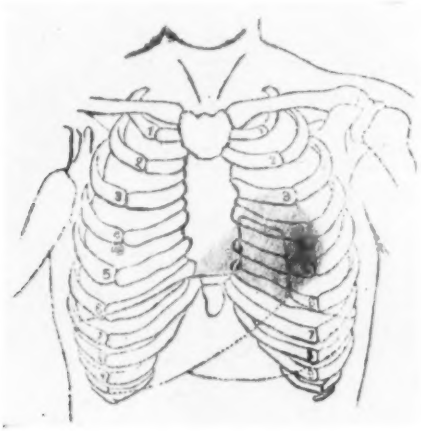

Fig. 1.—The area of pulsatory heaving is indicated by shading. The pulsation was most striking at the level of the fourth intercostal space in the left mid-clavicular line; it extended cranially to the third and caudally to the sixth rib, and reached the sternum medially.

Percussion revealed marked dullness over the sternum below the attachment of the third costal cartilage. Distinct dullness for a distance of about 3 cm. was also observed in the fifth right intercostal space adjacent to the sternum. On the left side there was no abnormal dullness in the second intercostal space, but marked dullness was found in the third intercostal space, covering an area of about 6 cm. In the fourth and fifth left intercostal spaces there was flatness which extended from the sternum to the left midclavicular line.

On auscultation, feeble heart sounds and a faint systolic murmur were heard over the point of maximum prominence in the fourth intercostal space. The second heart sound was louder than the first. In the second right intercostal space an accentuated second sound and a short, rather loud, systolic murmur were audible, in addition to a soft bruit of whistling character. The musical murmur was transmitted to the lower end of the sternum and second left intercostal space. It was not influenced by posture or respiration. No thrills were palpable over the chest. The pulsation in the carotid and radial arteries was feeble, but there was no pulse difference in the symmetrical arteries. The wall of the radial artery was soft, and the blood pressure 100/80 mm. Hg.

The abdomen was not distended. The liver extended about 3 cm. below the costal arch in the right mid-clavicular line; the spleen was not palpable. The urine was normal except for an increase in the amount of urobilinogen. The Wassermann reaction was positive. The electrocardiogram showed right axis deviation and normal sinus rhythm.

The roentgenologic abnormalities were unusual (only an orthodiagram was available, Fig. 2). The cardiac silhouette was bizarre, especially at the left border, where an irregular, approximately pear-shaped mass, with sharp outlines, seemed to be adherent. The contour of the left ventricle could not be differentiated from this abnormal shadow. The aorta appeared slightly dilated; its arch and descending portion could be readily differentiated from the abnormal mass at the left of the silhouette. The trachea showed marked deviation to the right. The radiologist thought that the abnormal shadow was caused by a mass adjacent to the heart at the left, and suggested the possibility of an encapsulated pericardial effusion. However, aneurysm of the aorta could not be excluded, although it seemed less likely because of the site of this abnormal shadow.

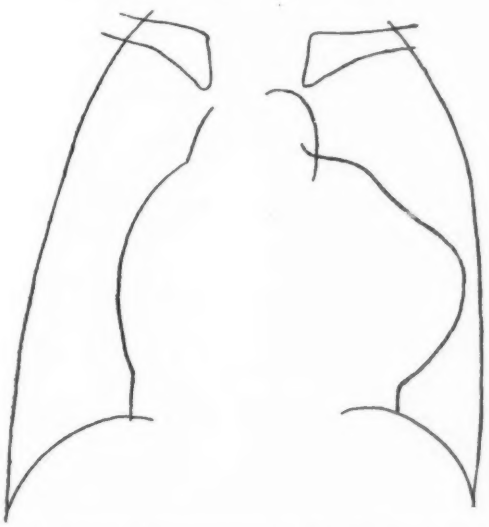

Fig. 2.—Orthodiagram, showing enlargement of the cardiovascular silhouette to the left, with a bizarre shape of the left border.

The history and clinical observations did not lend support to the assumption of encapsulated pericardial effusion. The broad pulsation in the precordial area aroused suspicion of a cardiac aneurysm,[1] to which the anginal attacks could also be attributed. However, the electrocardiogram did not support this opinion. The bizarre bulge at the left side of the roentgenologic silhouette started at the attachment of the second costal cartilage, i.e., at a higher level than is usual for a cardiac aneurysm. Also, there were symptoms pointing to erosion of ribs, which is not known to be caused by cardiac aneurysm. The same is true for bronchostenosis, which was distinctly manifest in our case. All the symptoms and signs that we had observed could be accounted for by an aneurysm of a large vessel, and this diagnosis was supported by the history of syphilis. The localization at the left of the sternum drew our attention to the pulmonary artery. However, aneurysms of the pulmonary artery are usually characterized by pulsations in the second intercostal space[2]; dilatations large enough to cause a pulsation in the third and fourth intercostal

spaces have not, as far as we know, been reported. Hence, aneurysm of the aorta, with unusual localization, seemed the most likely pathologic condition. Since on roentgenologic examination the arch and descending part of the aorta could be differentiated from the abnormal shadow, it seemed most probable that the aneurysm was of the ascending aorta, and that it had extended toward the left and displaced the heart.

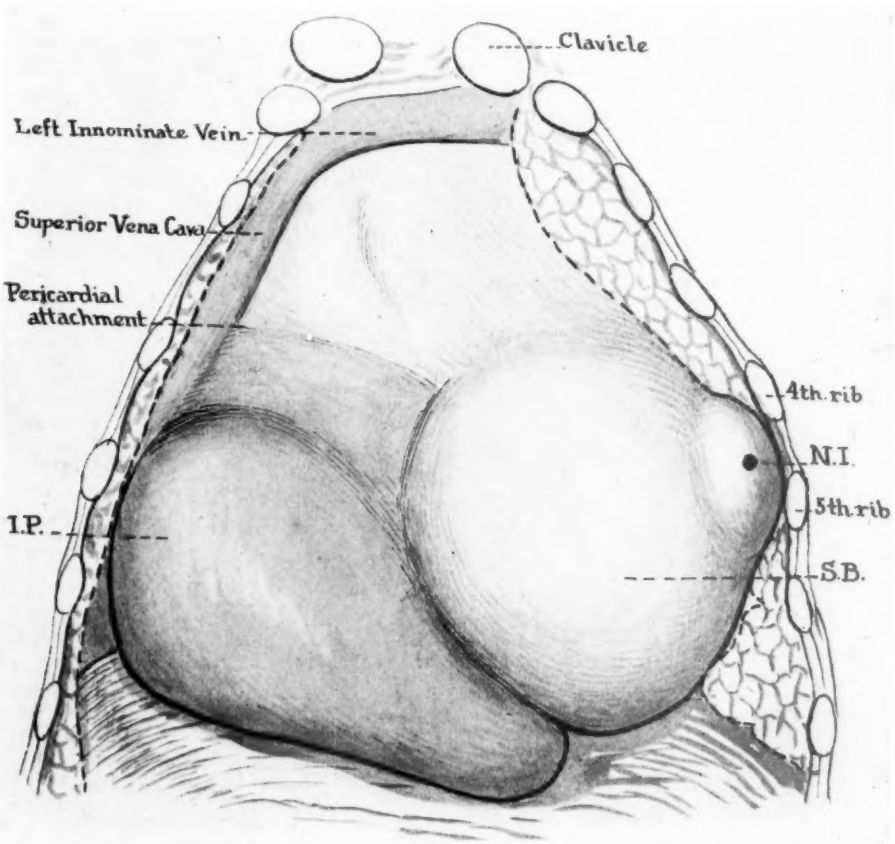

Fig. 3.—The anterior mediastinum after removal of the greater part of the anterior thoracic wall. The lungs are forced laterally and dorsad by the enlarged mediastinum. A large, semispherical bulge is visible on the left side, protruding against the fourth and fifth ribs. A needle that was inserted into the chest vertically at the area of the greatest convexity of the precordium pierced the bulge at "N.I." To the right, an irregular, dark-blue prominence is visible, extending up to a horizontal line (attachment of the pericardium) running about 2 cm. above the bulge. *I.P.*, Irregular prominence; *N.I.*, point of needle insertion; *S.B.*, semispherical bulge.

The patient's condition improved after a few days' rest in bed; the sensation of soreness in the precordium diminished and the dyspnea was less distressing. The patient insisted on leaving the hospital, and died suddenly a few days later.

Necropsy revealed marked enlargement of the anterior mediastinum (Fig. 3), which forced the lungs on either side laterad and dorsally. The mediastinum displayed two prominences. One, at the left, was semispherical, and protruded between the fourth and fifth ribs. It was separated by a furrow from an irregular bulge that made up the lower part of the right half of the mediastinum. Here there was a blue,

translucent discoloration up to a horizontal line which ran about 2 cm. above the irregular bulge. At the right and cranially the dark translucent band of the superior vena cava and left innominate veins was visible.

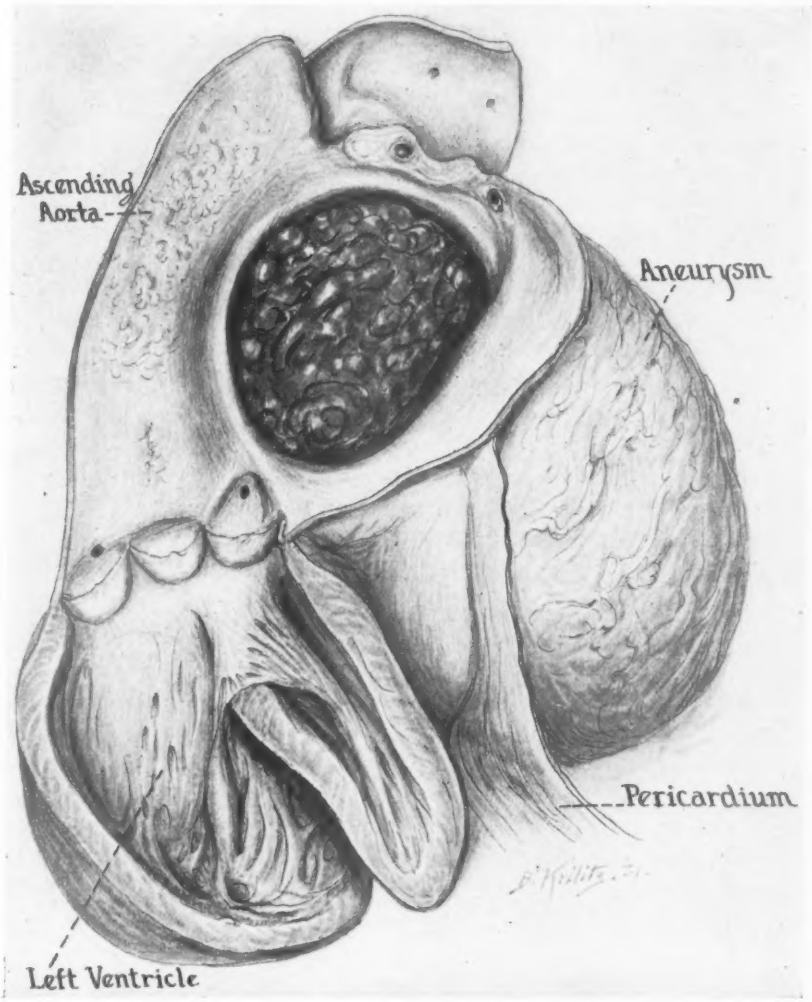

Fig. 4.—The left ventricle and the ascending part of the aorta have been opened. A large, round opening in the left wall of the aorta leads into an aneurysmal sac larger than a man's fist. The other portions of the aortic wall display remarkably little change. The left coronary orifice is pulled upward by the traction of the aneurysm. Note the close relationship of the aneurysm to the left coronary artery. The medial portion of the aneurysm is covered by the pericardium; the heart is displaced to the right.

The left semispherical prominence, which corresponded to the bulge observed clinically in the precordium, and seemed to be caused by the pericardium, was opened first. It contained a large amount of blood clots around a large, centrally located thrombus. The irregular bulge at the right side was formed by the heart and pericardium (Fig. 4). The pericardial sac was filled with a large quantity of blood, partly fluid and partly clotted; this was responsible for the translucent, blue discoloration. The heart was of normal size, its walls were not hypertrophied,

and the valves were intact. The intima of the ascending aorta showed slight scarring caused by syphilitic aortitis. At the left border of the aorta there was a circular opening, measuring 7 cm. in diameter, which led into an aneurysmal sac. The aneurysm was larger than a man's fist; it was filled with blood clots enclosing a large thrombus (as described above). This aneurysm had produced the semispherical bulge at the left half of the mediastinum. Expanding to the left and caudad, it had displaced the heart to the right and forced its left margin dorsad, thus causing a rotation of the heart from right to left (as seen from the front). The aneurysm was partly covered by the pericardium. A small perforation, just large enough to admit a thick probe, and leading into the pericardial cavity, was discovered at the lower border of the aneurysmal sac. The coronary orifices were of normal size. The left coronary ostium was displaced cranially by the traction of the aneurysm.

COMMENT

Extraordinary anatomic conditions, which occur only exceptionally, were responsible in our case for the unusual situation of the aortic aneurysm. There was remarkably little involvement of the wall of the aorta by syphilitic infiltration and destruction, except for a sharply limited circular area at the left border. This region was gradually stretched and distended, and the resulting aneurysm had expanded to the left and caudad, displacing the heart and causing it to rotate from right to left. This rotation produced a deviation of the electrical axis to the right in the electrocardiogram. Other sequelae of the aneurysm were compression of the left bronchus, resulting in dyspnea, diminished breath sounds over the left lung, and stridulous breathing; the anginal pains were caused by syphilitic inflammation of the aortic wall and pressure of the aneurysm on neighboring structures. The explanation of the attacks of pulmonary edema is more difficult, for such common causes as hypertension and aortic valve lesions were absent. There was no extension of the syphilitic infiltration to the valves of the aorta. However, the close topographic relationship of the aneurysmal tumor to the left coronary artery and to the heart suggests that pressure on the coronary artery and possibly on the left ventricle was responsible for left-sided heart failure and attacks of pulmonary edema.

SUMMARY

A case of syphilitic aortitis is presented, with almost exclusive involvement of the left side of the ascending aorta. A huge aneurysm developed to the left and extended caudad to the precordial region. It displaced the heart to the right and caused a rotation of the heart from right to left; this resulted in right axis deviation in the electrocardiogram. The aneurysm produced a broad pulsation and eroded several ribs in the precordial area between the third and sixth ribs.

REFERENCES

1. Dressler, W., and Pfeiffer, R.: Cardiac Aneurysm, A Report of Ten Cases, Ann. Int. Med. **14**: 100, 1940.
2. Henschen, S. E.: Das Aneurysma der Arteria pulmonalis, Samml. klin. Vortr. von Volkmann. N.F. No. 422-423, Inn. Med. p. 126, 1906.

Abstracts and Reviews

Selected Abstracts

Fishback, D. B., Guttman, S. A., and Abramson, E. B.: An Objective Method of Determining Blood Velocity (Fluorescein Method). Am. J. M. Sc. 203: 535, 1942.

A new objective circulation time test has been described, using fluorescein.

The data obtained indicate that the method is reasonably simple, not harmful to the patient, and reliable as indicated by comparison with other methods.

This method is of particular advantage in determining the blood velocity in small children, comatose, anesthetized, mentally ill, and moribund patients.

In patients with normal hearts or fully compensated cardiac disease, the circulation time varied from seven to 15.6 seconds. In another group of patients with cardiac disease undergoing decompensation, the circulation time varied from sixteen to twenty-five seconds, one being forty-five seconds.

AUTHORS.

Mahaim, E., and Winston, M. R.: Researches on the Comparative Anatomy and the Experimental Pathology of the Superior Connections of Bundle His-Tawara. Cardiologia 5: 189, 1941.

The His-Tawara bundle is not completely isolated from the musculature of the ventricular septum. There exist delicate connections which unite it to the upper part of the ventricular septum.

These upper connections are always to be found in man and the following animals: sheep, calf, dog, cat, rabbit. They are dispersed, varying in their caliber and topography. They are mostly direct, sometimes indirect and sometimes instantaneous. It is possible to identify them only in an uninterrupted series of slides.

These upper connections are of functional importance in physiopathology. They explain the lack of auriculo-ventricular block when both branches are destroyed simultaneously (bloc bilatéral manqué). The experimentation confirms the existence of this para-specific septal conduction.

In physiopathology these upper connections assume the functions of a substitutional organ. They explain the contradictions which occur in the anatomoclinical researches on bundle branch block.

In the normal cardiac contraction these upper connections probably assure a direct conduction between the specific tissue and the musculature of the upper part of the ventricular septum, in a region which does not directly communicate with Purkinje's terminal network.

AUTHORS.

Mackby, M. J.: Cephalic Bruit. A Review of the Literature and a Report of Six Cases. Am. J. Surg. **55**: 534, 1942.

It appears that cranial auscultation is a "near forgotten art." This method of examination is seldom employed by the average practitioner although simple of execution, and from such an examination one may derive valuable information. The pertinent features of the subject as recorded in the literature have been reviewed. Six examples of intracranial bruit occurring in patients harboring intracranial lesions have been reported in order to illustrate some of the pathologic states that may result in a bruit. In an endeavor to estimate the frequency of occurrence of this abnormal physical finding in persons not exhibiting signs of intracranial disturbances, the heads of 250 persons were auscultated. Cephalic bruit was demonstrated in only three instances (0.012 per cent) and in two of these cases, there was a murmur audible over the heart, the great vessels of the neck and the head. From evidence at hand, it seems logical to conclude that a cephalic bruit in any individual merits careful consideration and further investigation of the possible presence of an organic intracranial lesion.

AUTHOR.

Gregg, D. E., Shipley, R. E., Eckstein, R. W., Rotta, A., and Wearn, J. T.: Measurement of Mean Blood Flow in Arteries and Veins by Means of the Rotameter. Proc. Soc. Exper. Biol. & Med. **49**: 267-72, 1942.

The rotameter has been used to measure cardiac input and mean blood flow in the arteries and veins of the anesthetized dog. Typical records are shown. Tests indicate that in routine use the instrument will give reliable blood flow values with an error of less than 10 per cent. Its use enables the experimenter to determine at a glance the moment-to-moment flow during the time that flow is actually being measured, an advantage not possessed by any other known method. The rotameter is so simple in operation that it should also serve a very useful purpose for the measurement of blood flows in student experiments in the classroom for which as yet no simple and reliable method has been available.

AUTHORS.

Berghoff, R. S., Geraci, A. S., and Hirsch, D. A.: Senile Ectasy: A Clinical Study of the Aging Human Heart (Observations on Four Hundred Patients). Illinois M. J. **81**: 97, 1942.

This is a preliminary report of an investigation of four hundred of a total of one thousand cardiacs in the age group of fifty to eighty years. The material gathered consumed five and one-half years and embodies case histories, physical examinations, percussion measurements checked by telefluoroscopies and electrocardiograms. This incomplete study led to the following conclusions:

The most common forms of heart disease encountered in senescence are arteriosclerotic, hypertensive, syphilitic, rheumatic, and thyroid. The earliest subjective symptoms are dyspnea, heart consciousness, and pain. The outstanding and most important diagnostic physical sign is altered configuration of the heart. Percussion carefully carried out is reliable and has greater diagnostic value than auscultation. Telefluoroscopy is a simple, economical and practical diagnostic adjunct to percussion. The electrocardiograph furnishes more help in this age group than in any other types of heart disease. It is possible and practical to differentiate clinically three different stages of coronary disease. A fair working knowledge concerning the immediate prognosis of the various individual types of heart disease encountered in senile individuals has been presented.

AUTHORS.

Robb, J. S., and Robb, R. C.: Hypertension Electrocardiograms Experimentally Produced and Anatomically Explained. I. Cor Pulmonale. Am. J. M. Sc. 203: 625, 1942.

Electrocardiograms taken in experimental right heart failure agree in form with those of previous authors.

Whatever the cause, pulmonary hypertension, if immediately great, may produce acute right heart dilatation, or if sufficiently prolonged, results in right heart hypertrophy and eventually in failure.

The essential mechanism of failure consists in the progressive stretching of the three component muscles of the right ventricle. The weakest area at the right apex is formed by the superficial sinospiral muscle and strain of this muscle is heralded by some elevation of RS-T in all leads. A second weak area, the superficial bulbospiral portion of the apex, becomes involved and this is recognized by further elevation of RS-T in Leads II and III and coincident depression of S-T in Lead I. Widening at the base indicates failure of the deep sinospiral and is evidenced by marked depression of RS-T in Leads II and III, and either elevation or depression of RS-T in Lead I, depending on the degree of concomitant superficial bulbospiral involvement.

It is immaterial whether the exciting cause of muscle failure is rise of pressure within the right heart or whether failure is secondary to asphyxia produced either directly or reflexly. When these muscles are under tension and unduly stretched, the same electrocardiographic picture is produced as if the muscle were infarcted or otherwise damaged.

Because these muscles fail consecutively and because damage to each has its own effect on the electrocardiogram, and especially because there may have been pre-existing disease (or effects due to drug action), a valid explanation is available for the great variation in clinical electrocardiograms during an attack of cor pulmonale.

In these experiments, with the chest open, a dilated right heart was not associated with right axis deviation.

The McGinn-White type of electrocardiogram is probably associated with a moderately severe degree of rise and intracardiac pressure, stretching all three of the component muscles. When intracardiac pressure is dangerously increased, all S-T intervals are depressed in addition to some one or all of the changes described by McGinn and White, or Rösler.

If intracardiac pressure increases slowly, and not too greatly, the electrocardiogram may be wholly unaffected, or if the pressure increases are rapid and extreme, any combination of muscle injury pictures may occur, thus accounting for the variable reports concerning electrocardiograms in pulmonary embolism and hypertension.

The employment of muscle bundle localization may serve to increase the value of electrocardiograms in the recognition, treatment, and prognosis of cor pulmonale.

AUTHORS.

Carrillo, E. G.: Bifid R Wave in Derivation II. With a Note on the Electrocardiogram in Pituitary Basophilism. Rev. argent. de cardiol. 8: 401, 1942.

A case of pituitary basophilism (Cushing's syndrome) is described. The patient showed signs of myocardial weakness and died of a cerebral hemorrhage. In the electrocardiogram a bifid R wave in Lead II was observed. The pathologic significance of this electrocardiographic abnormality is insisted upon.

AUTHOR.

Robb, J. S., and Robb, R. G.: Hypertension Electrocardiograms Experimentally Produced and Anatomically Explained. II. Left Ventricular Strain. Am. J. M. Sc. **203**: 634, 1942.

Because in acute experiments on young animals no hypertrophy and myocardial damage (in the sense of infarct or connective tissue replacement) is present, one must attribute the various results to change in size of the ventricles dependent upon "strain," that is increased intraventricular pressure with dilatation (rather than hypertrophy).

Such a stretching of the musculature demonstrably alters conduction even to the point of causing ventricular fibrillation.

Either development of an injury current within a single muscle band or differential slowing of conduction (including recovery) may be regarded as the essential factor resulting in the characteristic electrocardiograms.

These S-T shifts in the electrocardiogram, caused by putting strain upon the individual muscle bundles, are the same as those produced by experimental infarction of the same muscle bundles.

Acute centralized systemic hypertension, experimentally induced, initiates a series of electrocardiographic changes reflecting the severity of the disturbance. The left ventricle is enclosed by four muscle masses which give way in sequence: the superficial sinospiral first, the superficial bulbospiral next, later the deep sinospiral muscle, and in extremis, the deep bulbospiral muscle. The authors' clinical experience parallels the animal data.

AUTHORS.

Morelli, A. C.: Diagnostic Tomography of Stenosis of the Isthmus of the Aorta and of Persistence of the Arterial Canal. Rev. argent. de cardiol. **8**: 371, 1942.

The author modifies his method of extrarapid tomography in order to study the posterior mediastinus. He uses short exposures (0.1 sec.), medium voltage, high amperage, small fields, antidifusor and horizontal dispersion. With this technique he has been able to visualize an aortic coaretation showing all its pathological characteristics. A comparative study was made with a case of angulation of the aorta. In two cases of persistence of the ductus arteriosus, the ductus was seen as a shadow uniting the aortic knob with the left branch of the pulmonary artery. This shadow has also been seen in apparently normal persons, that had, however, a dilatation of the pulmonary artery. It is suggested that these latter cases correspond to those in which there is a persistence of the ductus arteriosus without continuous murmur, as observed by Abbott in one-fifth of her cases.

AUTHOR.

Weisman, S. J.: Congenital Idiopathic Cardiac Hypertrophy. Arch. Path. **33**: 365, 1942.

Congenital idiopathic cardiac hypertrophy is enlargement of the heart by hypertrophy and dilation, associated frequently with thickening of the endocardium. The true cases, according to Kugel and Stoloff, show no myocardial changes, although perivascular fibrosis has been described frequently by others. No other lesion or anomaly is present in the true cases. Too few cases of anomaly of the coronary circulation have been described along with idiopathic hypertrophy to support any causal relation. When such anomaly is present, the resulting changes have not been the same as in true idiopathic hypertrophy. It seems logical to assume that the association of the two defects is accidental. Fetal myocarditis has not yet been proved to be the etiologic factor in the hypertrophy. Although, as knowledge of

abnormal conditions of the infant heart increases, fewer cases of cardiac hypertrophy are considered cases of idiopathic hypertrophy, there still remain many which cannot be explained.

The author reports two cases with findings at autopsy. No mention is made of the part played by glycogen storage dysfunction in this type of heart lesion.

AUTHOR.

Cushing, E. H., Feil, H. S., Stanton, E. J., and Wartman, W. B.: Infarction of the Cardiac Auricles (Atria): Clinical, Pathological, and Experimental Studies. Brit. Heart J. 4: 17, 1942.

Infarction of the cardiac auricles (atria) was found in 17 per cent of 182 cases of myocardial infarction that were proved at autopsy. Abnormalities in the auricular complex of the electrocardiogram were present in 74 per cent of the cases of atrial infarction, but in only 9 per cent of all cases of infarction of the ventricles. Ligation of the atrial arteries in dogs produced abnormal auricular mechanism in only 6 out of 20 experiments. In 4 additional experiments there was a transient change in the contour of the P wave. Depression of the P-Q segment of the electrocardiogram was seen in 4 instances in which the atrial arteries were ligated. Abnormality in auricular mechanism is the most reliable clue to the clinical diagnosis of infarction of the atria.

AUTHORS.

Console, A. D.: Relation of Cardiac Lesions to the Clinical Course of Rheumatic Fever. Arch. Int. Med. **69**: 551, 1942.

Of 98 cases in which endocarditis or pericarditis, found at autopsy, had been preceded by a history of rheumatic fever with polyarthritis or other similar manifestations of disease, Aschoff bodies were found in all in which death occurred during the first decade of life, in 64 per cent of those in which it occurred during the second decade and in 11 per cent of those in which it occurred during a later decade.

When Aschoff bodies were found in the myocardium (28 cases) with 1 exception the interval between the last attack of polyarthritis and death was five months or less.

In 3 cases in which Aschoff bodies occurred in the myocardium there was no history of polyarthritis, chorea or other clinical evidence of acute rheumatic infection.

A curve of the frequency of death in cases in which the symptoms of rheumatic fever and cardiac lesions occurred at different age periods shows two distinct peaks, one in the first decades of life, corresponding with deaths from cardiac failure and the presence of Aschoff bodies in the myocardium, and the other between the ages of 40 and 60 years, associated with cardiac failure, deforming lesions of the valves and an absence of Aschoff bodies.

Minor degrees of valvular deformity preponderated in the first three decades of life, whereas advanced deformity was common in the later decades. Valvular deformity increased with the duration of the disease after the onset of symptoms but had no constant relation to the number of attacks or to the age at onset.

AUTHOR.

Mainzer, F., and Krause, M.: The Electrocardiogram in the Bronchial Asthma Paroxysm. Cardiologia **5**: 261, 1941.

In 8 out of 16 patients with bronchial asthma the electrocardiographic tracings were found to be altered during the asthmatic paroxysm. The deformations present were: a low ventricular complex, notching within the ventricular complex

and particularly deformation of S-T and T. Moreover, as a rule, there was also tachycardia (120 a minute). Neither the electrocardiographic changes nor tachycardia disappeared, at least in some cases, until a lapse of several days after the attack.

Changes in the position of the heart can be excluded from bringing out the electrocardiographic phenomena; the alterations are considered to be due to myocardial anoxemia. The anoxemia is deemed to be brought about by insufficient O_2-saturation of the arterial blood as well as a reduced coronary circulation through hemodynamic disturbances or nervous stimuli (increased arterial pressure in the pulmonary circulation, increased vagal tone); tachycardia may also be active on these lines.

Sometimes neither the tachycardia nor the changes of the electrocardiographic curve disappeared until after some considerable time. From this fact (which we have not had the opportunity of studying in detail) we may conclude that the cardiac lesion produced by the asthmatic attack cannot be considered as being merely mechanical in nature. It is highly probable that the asthmatic paroxysm leaves the same marks upon the myocardium as other transitory anoxemic conditions do (angina pectoris attack, CO poisoning, muscular exertion in anemic persons).

In this way it becomes clear that the chronic circulatory disturbance developing during the course of bronchial asthma may be explained as well by the effect of recurring attacks of anoxemia on the myocardium as by mechanical overstrain imposed on the pulmonary circulation.

AUTHORS.

McPhedran, H.: Cardiovascular Changes in Toxic Goiter. Canad. M. A. J. 46: 471, 1942.

Reviews the cardiovascular changes found in connection with toxic goiter. From 1934 to 1940 inclusive, there have been treated in our wards at St. Michael's Hospital 115 cases diagnosed as toxic goiter and operated upon as such. A careful analysis of these cases from the cardiovascular standpoint has been made, and the result of this survey is herewith presented.

Of the total of 116 cases, 56 cases were found to present abnormal cardiovascular findings.

In this latter group, 19, or 33.9 per cent, were found at or below 40, and 37, or 66.1 per cent, above 40 years of age, with the largest group of all between 50 and 60 years. There were 16 males and 40 females.

AUTHOR.

Shelburne, S., Hawley, J. L., and McGee, A. S.: Retinal Arteriovenous Nicking: Relation to Enlargement of the Heart in Ambulatory Patients With Hypertension. Arch. Int. Med. 69: 213, 1941.

The authors were able to show by their study of 317 patients with hypertension that retinal arteriovenous nicking is so closely related to enlargement of the heart that if this lesion is found one may expect to find an enlarged heart. Furthermore, if this lesion is found in a patient with enlargement of the heart, the latter condition can be accounted for by hypertension, even if the blood pressure is normal at the time of examination. It may also be stated that if the heart of a hypertensive patient is enlarged and no arteriovenous nicking is found, the enlargement is not likely to be due to hypertension alone and a careful search for other lesions, such as those of severe coronary arterial disease, syphilis or rheumatic fever, is clearly indicated.

There is apparently no relation between the early change in the retinal arteries, which the authors have designated early arteriovenous nicking, and enlargement of the heart, but the later change, which they have called moderate arteriovenous nicking, is definitely related to enlargement of the heart, though not so closely as the fully developed lesion (definite arteriovenous nicking).

Arteriovenous nicking is important in the differentiation of the chronic nephritis associated with late hypertension and chronic glomerulonephritis.

It is hoped that this study will help to show the importance of careful observation of the changes in the retinal vessels and the necessity for more accurate description. There are too many reports, even from the best institutions, in which retinal arteriosclerosis is evaluated as 4 plus or grade 3 but the lesions are not described. Such a notation is meaningless. It is much more valuable to state whether arteriovenous nicking, extremely narrow arteries, changes in the caliber in arteries, etc., are present.

AUTHORS.

Ray, B. S.: Cerebral Arteriovenous Aneurysms. Surg., Gynec. & Obst. 73: 615, 1941.

Observations on six patients having cerebral arteriovenous aneurysms substantiate the conclusion that these lesions are congenital and can be identified by the clinical signs and symptoms they produce and by their appearance when exposed at the operating table.

A bruit heard on auscultation over some part of the head, the eyeballs, and the carotid arteries in the neck, is a characteristic sign. This, in conjunction with Jacksonian convulsions or unilateral motor and sensory disturbances, is usually sufficient to permit a diagnosis to be made.

Changes in the skull that may be shown on roentgenogram include slight signs of increased intracranial pressure, increased vascularity of the skull, deepening of the grooves for the middle meningeal arteries, local atrophy of the inner table from direct pressure of the vessels of the aneurysm, enlargement of the head, and calcification in the lesion.

Air studies may be relied upon, in many instances, to demonstrate abnormalities in the ventricles and subarachnoid spaces. Encephalography in such cases is safer than ventriculography.

Cerebral angiography is indicated in order to visualize the extent and the location of the lesion.

The collateral circulation is extensive. It involves anastomosis between the external and internal carotid arterial systems, principally through the orbit and through the meninges.

The effects of the aneurysm upon the general cardiovascular system are variable but not necessarily serious.

Headache, localized on the side of the lesion, is usually due to pain arising in the dilated arteries, chiefly in branches of the external carotid artery.

Reasonably safe methods of treatment include exploratory osteoplastic operation and decompression, successive ligation of the carotid arteries in the neck, and roentgenotherapy. None can be relied upon to be curative, but used alone or in combination they may be beneficial.

Ligation of carotid arteries is safer in persons with cerebral arteriovenous aneurysms than in others because of the rich collateral circulation.

Direct operative attack upon the lesions is dangerous but might be indicated in selected cases.

AUTHOR.

Fulton, G. P., and Lutz, B. R.: Smooth Muscle Motor-Units in Small Blood Vessels. Am. J. Physiol. **135**: 531, 1942.

Stimulation of minute nerves, with a microelectrode, produced spatially limited vascular responses, generally dilatation followed by constriction, in the small blood vessels of the retrolingual membrane of the frog, *Rana pipiens*. The limited responses suggest the concept of smooth muscle motor-units in small blood vessels.

Seymour, W. B., Pritchard, W. H., Longley, L. P., and Hayman, J. M.: Cardiac Output, Blood and Interstitial Fluid Volumes, Total Circulating Serum Protein, and Kidney Function During Cardiac Failure and After Improvement. J. Clin. Investigation **21**: 229, 1942.

Estimations of cardiac output, volume of blood and interstitial fluid, concentration and total amount of plasma proteins, and of inulin, phenol red and urea clearances were made on six patients with congestive heart failure and again after restoration of compensation by digitalis and diuretics.

Cardiac output and stroke volume increased with improvement in all cases. The mean minute output during failure was 31 per cent less than after improvement. Effective peripheral resistance decreased coincidentally with improvement.

Blood and serum volumes also decreased with recovery, the mean change in blood volume being 1.15 liters or 25 per cent, and in serum volume 0.92 liter or 35 per cent of the volumes during failure. In spite of a marked decrease in the volume of intercellular fluid, the mean value after restoration of compensation was 32 per cent total body weight, or almost 50 per cent above normal.

While the concentration of serum proteins, particularly of the globulin fraction, increased with clinical improvement, the total amount of circulating protein decreased, due almost entirely to a decrease in serum albumin.

Inulin clearance showed no significant change with improvement, while phenol red clearance increased to approximately the same degree as cardiac output.

AUTHORS.

Theis, F. V., and Freeland, M. R.: Thromboangiitis Obliterans. Surgery **11**: 101, 1942.

The clinical results in the treatment of the biochemical blood changes in acute or active thromboangiitis obliterans with sodium tetrathionate or sodium thiosulfate and of the peripheral circulatory deficiency due to arterial thromboses with pavaex treatment have been most encouraging.

Deficient oxygenation of the arterial blood was usually present during the active stage of the disease. Following treatment for two to six weeks, the increased oxygenation of the arterial blood was accompanied by clinical improvement and in some cases by clinical recovery (five years).

The oxygenation of the arterial blood in the majority of patients with thromboangiitis obliterans which we studied was affected by smoking.

AUTHORS.

Dublin, L. I., and Marks, H. H.: A Note on the Inheritance of Cardiovascular Disease—Results of Life Insurance Investigations. J. Mt. Sinai Hosp. **8**: 482, 1942.

These several studies point to a definite relationship between parents and offspring with respect to cardiovascular diseases. The clinical studies have generally shown that among patients with any form or symptom of the diseases, there is a high incidence of these diseases or symptoms in the parental history. In the insurance

studies, it has been found that the total mortality of persons with a family history of these conditions has ranged from approximately normal to well above normal, but in every study in which the death rate from chronic cardiovascular diseases was considered, the mortality from them has been above average. In none of the studies was the mortality of these cases low, even though on the basis of the survivorship of the parents to advanced ages, the history was favorable. It is fair to conclude, therefore, that these studies indicate a familial relationship in the cardiovascular diseases.

The nature of this association cannot be brought out with any great exactness from insurance studies, or indeed from most of the material thus far collected on the subject. It is not likely that this association is a matter of direct inheritance of faulty cardiac or vascular structure in most instances, but rather that a number of factors are involved. For example, insurance studies have shown that the mortality from the cardiovascular-renal diseases is appreciably higher among the obese than among persons of slighter build. Since there are strong hereditary factors in body build or structure, the effect of heredity as regards the incidence of cardiovascular disease may be an indirect one.

The mortality from cardiovascular diseases among those with a family record of early deaths from such diseases is, however, not free from the influence of non-hereditary factors which tend to raise the mortality from them. For example, individuals orphaned at a relatively early age, regardless of the cause of death of the parents, are subject to deleterious environmental conditions associated with broken homes. Among children in such families, the frequency of infections leading to early cardiovascular or renal disease is relatively high. Moreover, many of these children must work at an early age and, consequently, often at unskilled or semi-skilled occupations, and among persons in such occupations the mortality from cardiovascular-renal diseases is appreciably above average.

The question may properly be raised whether a familial association with any cardiovascular disease or its symptoms is unfavorable to longevity. For, if such relationship involved no diminution in longevity, this relationship, while of medical interest, would be of no great consequence. This is by no means the case. The presence of these diseases in abnormal frequency in the family history at an early age is often an indication of the existence of those factors which produce early vascular degeneration. This is indicated by the fact that the excess death rate from these diseases among the persons we have studied is not concentrated at the older ages, and at the longer durations of insurance, but is present at every age and apparently is relatively worse for the shorter durations than the longer ones. Consequently, a great proportion of the deaths of these persons with a poor family record of cardiovascular disease occurs at relatively young ages. A family record of this type must, therefore, be considered generally unfavorable to longevity.

AUTHORS.

Flaxman, N.: Clinical Value of Digitalis in Hypertensive Heart Failure. II. With Sinus Tachycardia. Am. J. M. Sc. 203: 747, 1942.

The study of 160 cases of hypertensive heart failure with sinus tachycardia is reported.

The cardiac rate is important as a prognostic sign, because the mortality among these patients, with the exception of A-V nodal rhythm, was the highest of all groups of hypertensives.

Exempted were those with isolated failure of the left ventricle where the mortality, due chiefly to coronary thrombosis, was only 11.3 per cent, as compared with the mortality of 37.7 per cent among those with the combined type of ventricular failure.

Congestive heart failure, the factor controllable by digitalis, was responsible for 34 (69 per cent) of the 49 deaths, but all of these were in patients who had the combined type of failure before the treatment was started.

Digitalis was administered to these hypertensive patients with rapid, regular cardiac rhythm not for its action on the rate, but to relieve the symptoms and signs of heart failure, which it did successfully in 70 per cent of the patients.

AUTHOR.

Wilkinson, K. D.: Two Cases of Digitalis Poisoning. Brit. Heart J. 4: 1, 1942.

Two cases of digitalis poisoning in patients with sinus rhythm are recorded. Each showed complete auriculoventricular dissociation; coupled beats; and marked abnormalities in the QRS-T complexes.

Recovery was slow and some degree of heart block persisted for twelve days after the digitalis was discontinued. One case showed bundle branch block as well as auriculoventricular block.

AUTHOR.

Kaltreider, N. L., Mencely, G. R., and Allen, J. R.: The Effect of Epinephrine on the Volume of the Blood. J. Clin. Investigation 21: 339, 1942.

Measurements were made at rest of the volume of the blood and its components, and variations in the volumes were followed after the subcutaneous injection of 1 c.c. of epinephrine (1:1000). Further observations included measurements of the blood hemoglobin and viscosity, serum proteins, venous and arterial pressures, velocity of the blood and pulse rate. These observations lead to the following conclusions:

In normal individuals, following the administration of epinephrine, there is a prompt and definite decrease in the plasma volume, which persists in most cases for at least 45 minutes. In the majority of cases there is a slight increase in the cell volume. These alterations are associated with an increase in blood hemoglobin and viscosity and serum proteins. Following the administration of the drug, the systolic pressure increased while the diastolic pressure fell slightly.

In the individuals who have polycythemia vera with splenomegaly, epinephrine causes a definite decrease in the plasma volume, a moderate increase in cell volume with little change in the total volume.

After the injection of epinephrine into 2 individuals whose spleens had been removed, there was a decrease in both blood and plasma volumes, accompanied by a slight decrease in the cell volume.

The effects of severe exercise and of epinephrine on the components of the blood volume are similar.

AUTHORS.

Allen, C. R., Stutzman, J. W., Slocum, H. C., and Orth, O. S.: Protection From Cyclopropane-Epinephrine Tachycardia by Various Drugs. Anesthesiology 2: 503, 1941.

Procaine, carbon dioxide, quinidine, morphine, ergotamine, F 883 (diethyl-amino-methyl-benzo-dioxane), and yohimbine have been studied for the prevention of cyclopropane-epinephrine tachycardia. These agents are all protective in proper dosages. The effective amounts per kilogram when administered intravenously are: procaine, 16 mg.; quinidine, 15 mg.; ergotamine, 1/6 mg.; F 883, 2.0 mg.; and yohimbine, 0.2 mg. The morphine dose was 8 mg. per Kg. when given subcutaneously. Twenty to 24 per cent carbon dioxide in the anesthetic mixture also gave protection.

It is believed that procaine, carbon dioxide, and quinidine give protection from cyclopropane-epinephrine tachycardia because of myocardial depression; F 883 and ergotamine, by their sympathicolytic action; yohimbine, through its adrenolytic action; and morphine, by producing either functional decerebration or myocardial depression.

AUTHORS.

Book Review

A INSUFICIÊNCIA CORONÁRIA: By Dr. Caio Benjamin Dias, Assistente de Clinica Propedeutica Medica da Faculdade de Medicina da U. M. G. Livraria Editora Paulo Bluhm, Belo Horizonte, 1941, 162 pages, 51 illustrations.

This is an up-to-date and well-written review on the concept of coronary insufficiency, and should be of value to readers of Portuguese who wish to acquaint themselves with the modern views on the subject. The monograph begins with a good summary of recent work on the anatomy and physiology of the coronary circulation, takes up the concept of coronary insufficiency, discusses the general electrocardiographic and anatomic changes, causes, and mechanisms, clinical manifestations, and then closes with a study of the electrocardiogram.

In the last chapter the author also gives his personal experience with exercise tests. The exercise consisted in the rapid climbing of 5 steps, 20 times in succession. Electrocardiograms were taken before and after exercise with the standard leads and Lead IV F. For a positive test the author relies on the following criteria: (1) inversion of the T wave in one or more leads, a diphasic T, or an exaggeration of a previously negative T; (2) depression of the S-T segment in one or more leads of more than 2 mm., especially when accompanied by such changes in the T wave as flattening, inversion, increase in negativity, or a diphasic T; (3) appearance of transitory intraventricular conduction defects or either auricular or ventricular extrasystoles from several foci. Seventy tests were performed on 60 subjects, 14 of whom were patients with coronary disease. The conclusions of the author corroborate the experience of others.

There are 13 drawings of electrocardiograms and 37 reproductions of electrocardiographic tracings. The majority of the illustrations are good. There is some evidence of careless editing, such as the absence of Fig. 5 and a serious misprint on page 40, where embolism of the coronary arteries is referred to as "pulmonary embolism." The bibliography lists 163 references.

RAFAEL DOMINGUEZ.

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